

DDR1 AND DDR2 INHIBITORS HAVING A DIHYDROBENZIMIDAZOLONE CORE

[0001] This invention relates to novel compounds and pharmaceutical compositions comprising the novel compounds. More specifically, the invention relates to compounds useful as inhibitors of discoidin domain receptor 1 (DDR1) and discoidin domain receptor 2 (DDR2). The compounds are particularly
5 useful in the treatment of cancer and fibrotic diseases

BACKGROUND

[0002] Discoidin Domain Receptors (DDRs) DDR1 and DDR2 are type 1 transmembrane Receptor Tyrosine Kinases (RTKs) with collagen receptor functionality (Vogel et al, Mol. Cell, 1997). DDRs contain characteristic collagen binding discoidin domains in the N-terminal extracellular domain. These domains
10 are preceded by an extracellular juxtamembrane domain, a single transmembrane domain, a cytosolic juxtamembrane domain and a catalytic kinase domain prior to a short C-terminal tail. Five isoforms of DDR1 (DDR1a-e) have been identified which arise from alternative splicing of the cytoplasmic region. No alternative isoforms of DDR2 have been identified. DDR1 and DDR2 have broadly (but not completely) mutually exclusive expression profiles in epithelial cell and stroma respectively. DDRs are
15 activated by binding to collagens with broad specificity but with distinct preference for certain collagen types. Upon activation DDRs are known to regulate cell adhesion, proliferation and remodelling of the extracellular matrix. It is recognised that DDRs are upregulated in response to cellular activity and many forms of tissue injury and as such DDRs are implicated in diseases including cancer, atherosclerosis as well as diseases characterised by fibrosis and inflammation. Inhibitors of DDR kinase activity may be of
20 benefit as therapeutic agents in these disease areas.

[0003] DDR1 and DDR2 overexpression and/or activation has been linked to multiple forms of cancer as summarised in a recent review (Elkamhawy et al, Int. J. Mol. Sci., 2021). Studies have shown that elevated DDR expression levels and/or mutations can be found in a number of cancer cell lines as well as primary tumour tissues including lung, pancreas, prostate, breast, brain, ovary, liver and others.
25 DDR1 was found to be a prognostic marker for non-small-cell lung carcinoma (NSCLC) patients. A recent study demonstrated that siRNA-mediated downregulation of DDR1 suppressed melanoma cell malignancy, migration, invasion, and survival. DDR1 protein was also found to be expressed in 63% of serous ovarian cancer tissue, but not in normal ovarian surface epithelium. Involvement of DDR1 in glioblastoma cell invasion and epithelial-mesenchymal transition (EMT) has also been demonstrated.
30 DDR1 expression was found in 50.5% of gastric cancer tissues. DDR1 was found to control triple-negative breast cancer growth by modulating tumour-infiltrating CD4+ and CD8+ T cells. There is also strong evidence indicating that DDR2 could be a potential biomarker and a molecular target for a variety of cancers. For instance, DDR2 overexpression was reported to contribute to NSCLC, thyroid carcinoma, Hodgkin's lymphoma, nasopharyngeal carcinomas, prostate cancer, as well as to head and
35 neck squamous cell carcinoma. According to studies DDR2 contributes to breast cancer metastasis by stabilizing the SNAIL1 protein. DDR2 has also been shown to be a favourable independent predictor of recurrence and outcome in primary breast cancers. In addition to the essential roles of the wild type of DDR in cancer pathology and prognosis, various mutations of DDR1 and/or DDR2 have also been reported in numerous types of cancer cells, for instance, G1486T(DDR1) and A496S(DDR1) in lung

cancer, N502S(DDR1), A533S(DDR1), and A803V(DDR1) in acute myeloid leukemia (AML), and S768R(DDR2) in squamous cell carcinoma. DDRs also play a role in cancer growth by controlling how tumour cells interact with their surrounding collagen matrix. This role of DDRs becomes more prominent when considering their role as extracellular matrix receptors. The extracellular matrix (ECM) confers structural properties to tissues around the tumour, as well as regulating cell proliferation, survival, migration, and invasion. The physiological interactions between tumour cells and their immediate microenvironment, represented by the extracellular matrix, are disrupted in metastatic cancers. As a key component of the tumour extracellular matrix, type I collagen shows high density and distorted architecture in malignant cancer, linking it to tumour formation and metastasis. Therefore, the discovery of DDRs as collagen receptors represents a new target in the regulation of tumour progression.

[0004] DDRs also appear to play a central role in the modulation of inflammation and fibrosis. Modulation of fibrosis and inflammation has been demonstrated in several organs including lung and kidney. In lung, DDR-1 deficient mice show reduced bleomycin induced pulmonary injury (Vogel et al, Am. J. Respir. Crit. Care Med., 2006) and both DDR1 and DDR2 have been demonstrated to have increased expression in patients with fibrotic lung disease (Bian et al, ERJ Open Res., 2016). In kidney, DDR1 expression is elevated in patients with lupus nephritis and Goodpasture's syndrome as well as mouse models of glomerulonephritis (Kerroch et al, FASEB journal, 2012) and in the tubules of mice that have undergone unilateral ureteral obstruction (UUO) (Guerrot et al, Am. J. Pathol., 2011). Several studies have demonstrated that DDR1-null mice are protected from angiotensin II-mediated proteinuria, glomerular fibrosis and inflammation as well as showing reduced collagen deposition, tubular macrophage infiltration and pro-inflammatory cytokine levels following the UUO procedure. Finally, COL3A3 KO mice (the mouse model for human Alport syndrome, crossed on to DDR1-null mice have mice have reduced renal fibrosis and inflammation as a consequence of reduced TGF- β mediated signalling and reduced levels of the pro-inflammatory cytokine IL-6 (Dorison, Cell Adhesion and Migration, 2018).

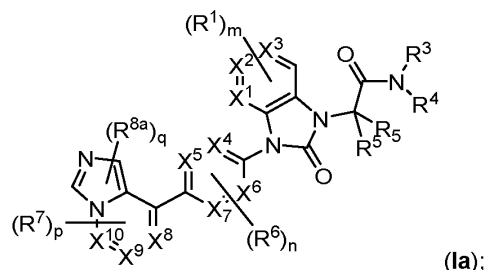
[0005] Small molecule inhibitors of DDR1 and DDR2 kinase activity have been disclosed in the prior art and inhibitory activity of DDR1 and/or DDR2 has been demonstrated to give rise to efficacious effects in mouse models of cancer and fibrotic disease (Richter et al, ACS Chem. Biol., 2019; Wang et al, J. Med. Chem., 2018; Zhu et al, J. Med. Chem., 2019). Such reports support the hypothesis that inhibitors of DDR kinase activity may be of benefit as therapeutic agents for the treatment of human cancer and fibrotic disease.

[0006] Furthermore, it is an aim of certain embodiments of this invention to provide new compounds useful in treating diseases such as cancer and fibrotic diseases. The compounds may be inhibitors of DDR1 and/or DDR2. It is an aim of certain embodiments of this invention to provide compounds which have comparable activity to existing DDR1 and/or DDR2 inhibitors. It is an aim of certain embodiments of this invention to provide compounds which have increased activity relative to existing DDR1 and/or DDR2 inhibitors.

[0007] Certain embodiments of the present invention satisfy some or all of the above aims.

BRIEF SUMMARY OF THE DISCLOSURE

[0008] The present invention relates to a compound of formula (Ia) or a pharmaceutically acceptable salt thereof:



5 wherein

X¹, X² and X³ are each independently selected from carbon and nitrogen, wherein at least two of X¹, X² and X³ are carbon;

X⁴, X⁵, X⁶ and X⁷ are each independently selected from carbon and nitrogen, wherein at least two of X⁴, X⁵, X⁶ and X⁷ are carbon;

10 X⁸, X⁹ and X¹⁰ are each independently selected from carbon and nitrogen, wherein at least two of X⁸, X⁹ and X¹⁰ are carbon;

R¹ is independently selected at each occurrence from halo, nitro, cyano, NR⁹R¹⁰, OR¹¹, SR⁹, SO₂NR⁹R⁹, SO₂R⁹, CO₂R⁹, C(O)R⁹, CONR⁹R⁹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl and cyclopropyl;

15 R³ is independently selected from H and C₁-C₄-alkyl;

R⁴ is independently selected from C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₀-C₄-alkylene-R^{4a}; wherein R^{4a} is independently selected from: C₃-C₈-cycloalkyl, phenyl, 5-, 6-, 9- or 10-membered heteroaryl and 4- to 10-membered heterocycloalkyl; wherein said heterocycloalkyl or heteroaryl group may be monocyclic or bicyclic; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with a single R¹² group and/or from 1 to 4 R¹³ groups and wherein said phenyl or heteroaryl group is optionally substituted with a single R¹² group and/or from 1 to 3 R¹⁴ groups;

20 or R³ and R⁴, together with the nitrogen atom to which they are attached together form a 4- to 10-membered heterocycloalkyl group or a 5-, or 9-membered heteroaryl group; wherein said heterocycloalkyl or heteroaryl group may be monocyclic or bicyclic; wherein said heterocycloalkyl group is optionally substituted with a single R¹² group and/or from 1 to 4 R¹³ groups and wherein said heteroaryl group is optionally substituted with a single R¹² group and/or from 1 to 3 R¹⁴ groups;

R⁵ is independently at each occurrence selected from H, halo and C₁-C₄-alkyl, or the two R⁵ groups and the carbon atom to which they are attached may together form a C₃-C₆ cycloalkyl ring;

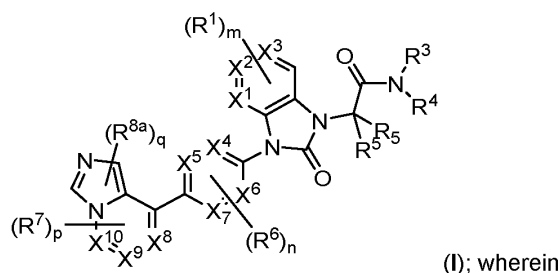
25 R⁶ is independently at each occurrence selected from halo, nitro, cyano, NR⁹R¹⁰, OR¹¹, SR⁹, SO₂NR⁹R⁹, SO₂R⁹, CO₂R⁹, C(O)R⁹, CONR⁹R⁹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl and cyclopropyl;

- R⁷ is independently at each occurrence selected from halo, nitro, cyano, NR⁹R¹⁰, OR¹¹, SR⁹, SO₂NR⁹R⁹, SO₂R⁹, CO₂R⁹, C(O)R⁹, CONR⁹R⁹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl and cyclopropyl;
- R^{8a} is independently selected from halo, nitro, cyano, NR⁹R¹⁰, OR¹¹, SR⁹, SO₂NR⁹R⁹, SO₂R⁹, CO₂R⁹, C(O)R⁹, CONR⁹R⁹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl and C₀-C₄-alkylene-R^{8c};
- R^{8c} is independently selected from C₃-C₆-cycloalkyl and 3- to 7-membered heterocycloalkyl; wherein said heterocycloalkyl group is attached to the C₀-C₄-alkylene via a carbon atom in the heterocycloalkyl ring; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R¹³ groups;
- R⁹ is independently at each occurrence selected from H and C₁-C₄-alkyl; or two R⁹ groups, together with the nitrogen atom to which they are attached together form a C₅-C₈-heterocycloalkyl group optionally substituted with from 0 to 4 R¹⁵ groups;
- R^{9a} is independently at each occurrence selected from H and C₁-C₄-alkyl;
- R¹⁰ is independently at each occurrence selected from H, C₁-C₄-alkyl, C(O)-C₁-C₄-alkyl and S(O)₂-C₁-C₄-alkyl; or R⁹ and R¹⁰, together with the nitrogen atom to which they are attached together form a C₅-C₈-heterocycloalkyl group optionally substituted with from 0 to 4 R¹⁵ groups;
- R¹¹ is independently at each occurrence selected from H, C₁-C₄-alkyl, C(O)-C₁-C₄-alkyl and C₁-C₄-haloalkyl;
- R¹² is independently selected from C₃-C₆-cycloalkyl, phenyl, 5- or 6- membered heteroaryl and 3- to 6-membered-heterocycloalkyl; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R¹³ groups and wherein said phenyl or heteroaryl group is optionally substituted with from 1 to 3 R¹⁴ groups;
- R¹³ is independently at each occurrence selected from =O, halo, nitro, cyano, NR⁹R¹⁰, OR¹¹, SR⁹, SO₂NR⁹R⁹, CO₂R⁹, C(O)R⁹, CONR⁹R⁹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with OR¹¹, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl, C₆-C₁₀-aryl, and C₃-C₆-cycloalkyl;
- R¹⁴ is independently at each occurrence selected from halo, nitro, cyano, NR⁹R¹⁰, OR¹¹, SR⁹, SO₂R⁹, SO₂NR⁹R¹⁰, CO₂R⁹, C(O)R⁹, CONR⁹R⁹, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl, C₁-C₄-alkyl substituted with OR¹¹, C₁-C₄-alkyl substituted with NR⁹R¹⁰ and cyclopropyl;
- R¹⁵ is independently at each occurrence selected from =O, halo, nitro, cyano, NR^{9a}R¹⁰, OR¹¹, SR⁹, SO₂NR^{9a}R⁹, CO₂R⁹, C(O)R⁹, CONR^{9a}R⁹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with OR¹¹, C₁-C₄-alkyl substituted with NR^{9a}R¹⁰, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl, C₆-C₁₀-aryl, and C₃-C₆-cycloalkyl;
- m is an integer selected from 0, 1, 2, 3 and 4;
- n is an integer selected from 0, 1, 2, 3 and 4;
- p is an integer selected from 0, 1, 2 and 3;
- q is an integer selected from 0, 1 and 2

wherein any of the aforementioned alkyl, alkylene or cyclopropyl groups is optionally substituted, where chemically possible, by 1 to 5 substituents which are each independently at each occurrence selected from the group consisting of: halo, oxo, fluoro, nitro, cyano, NR^aR^b, OR^a, SR^a, CO₂R^a,

C(O)R^a, CONR^aR^a, C₁-C₄-alkyl, C₁-C₄-haloalkyl and cyclopropyl; wherein R^a is independently at each occurrence selected from H, C₁-C₄-alkyl and C₁-C₄-haloalkyl; and R^b is independently at each occurrence selected from H, C₁-C₄-alkyl, C(O)-C₁-C₄-alkyl and S(O)₂-C₁-C₄-alkyl

[0009] The present invention relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof:



X¹, X² and X³ are each independently selected from carbon and nitrogen, wherein at least two of X¹, X² and X³ are carbon;

10 X⁴, X⁵, X⁶ and X⁷ are each independently selected from carbon and nitrogen, wherein at least two of X⁴, X⁵, X⁶ and X⁷ are carbon;

X⁸, X⁹ and X¹⁰ are each independently selected from carbon and nitrogen, wherein at least two of X⁸, X⁹ and X¹⁰ are carbon;

15 R¹ is independently selected at each occurrence from halo, nitro, cyano, NR⁹R¹⁰, OR¹¹, SR⁹, SO₂NR⁹R⁹, SO₂R⁹, CO₂R⁹, C(O)R⁹, CONR⁹R⁹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl and cyclopropyl;

R³ is independently selected from H and C₁-C₄-alkyl;

20 R⁴ is independently selected from C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₀-C₄-alkylene-R^{4a}; wherein R^{4a} is independently selected from: C₃-C₈-cycloalkyl, phenyl, 5-, 6-, 9- or 10-membered heteroaryl and 4- to 10-membered heterocycloalkyl; wherein said heterocycloalkyl or heteroaryl group may be monocyclic or bicyclic; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with a single R¹² group and/or from 1 to 4 R¹³ groups and wherein said phenyl or heteroaryl group is optionally substituted with a single R¹² group and/or from 1 to 3 R¹⁴ groups;

25 or R³ and R⁴, together with the nitrogen atom to which they are attached together form a 4- to 10-membered heterocycloalkyl group or a 5-, or 9-membered heteroaryl group; wherein said heterocycloalkyl or heteroaryl group may be monocyclic or bicyclic; wherein said heterocycloalkyl group is optionally substituted with a single R¹² group and/or from 1 to 4 R¹³ groups and wherein said heteroaryl group is optionally substituted with a single R¹² group and/or from 1 to 3 R¹⁴ groups;

30 R⁵ is independently at each occurrence selected from H, halo and C₁-C₄-alkyl, or the two R⁵ groups and the carbon atom to which they are attached may together form a C₃-C₆ cycloalkyl ring;

R⁸ is independently at each occurrence selected from halo, nitro, cyano, NR⁹R¹⁰, OR¹¹, SR⁹, SO₂NR⁹R⁹, SO₂R⁹, CO₂R⁹, C(O)R⁹, CONR⁹R⁹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl and cyclopropyl;

R⁷ is independently at each occurrence selected from halo, nitro, cyano, NR⁹R¹⁰, OR¹¹, SR⁹, SO₂NR⁹R⁹, SO₂R⁹, CO₂R⁹, C(O)R⁹, CONR⁹R⁹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl and cyclopropyl;

R^{8a} is independently selected from halo, nitro, cyano, NR⁹R¹⁰, OR¹¹, SR⁹, SO₂NR⁹R⁹, SO₂R⁹, CO₂R⁹, C(O)R⁹, CONR⁹R⁹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl and C₀-C₄-alkylene-R^{8c};

R^{8c} is independently selected from C₃-C₆-cycloalkyl and 3- to 7-membered heterocycloalkyl; wherein said heterocycloalkyl group is attached to the C₀-C₄-alkylene via a carbon atom in the heterocycloalkyl ring; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R¹³ groups;

R⁹ is independently at each occurrence selected from H and C₁-C₄-alkyl; or two R⁹ groups, together with the nitrogen atom to which they are attached together form a C₅-C₈-heterocycloalkyl group optionally substituted with from 0 to 4 R¹³ groups;

R¹⁰ is independently at each occurrence selected from H, C₁-C₄-alkyl, C(O)-C₁-C₄-alkyl and S(O)₂-C₁-C₄-alkyl; or R⁹ and R¹⁰, together with the nitrogen atom to which they are attached together form a C₅-C₈-heterocycloalkyl group optionally substituted with from 0 to 4 R¹³ groups;

R¹¹ is independently at each occurrence selected from H, C₁-C₄-alkyl, C(O)-C₁-C₄-alkyl and C₁-C₄-haloalkyl;

R¹² is independently selected from C₃-C₆-cycloalkyl, phenyl, 5- or 6- membered heteroaryl and 3- to 6-membered-heterocycloalkyl; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R¹³ groups and wherein said phenyl or heteroaryl group is optionally substituted with from 1 to 3 R¹⁴ groups;

R¹³ is independently at each occurrence selected from =O, halo, nitro, cyano, NR⁸R⁹, OR¹⁴, SR⁸, SO₂NR⁸R⁸, CO₂R⁸, C(O)R⁸, CONR⁸R⁸, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with OR¹¹, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl, C₆-C₁₀-aryl, and C₃-C₆-cycloalkyl;

R¹⁴ is independently at each occurrence selected from halo, nitro, cyano, NR⁸R⁹, OR¹⁰, SR⁸, SO₂R⁸, SO₂NR⁸R⁸, CO₂R⁸, C(O)R⁸, CONR⁸R⁸, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl, C₁-C₄-alkyl substituted with OR¹¹, C₁-C₄-alkyl substituted with NR⁸R⁹ and cyclopropyl;

m is an integer selected from 0, 1, 2, 3 and 4;

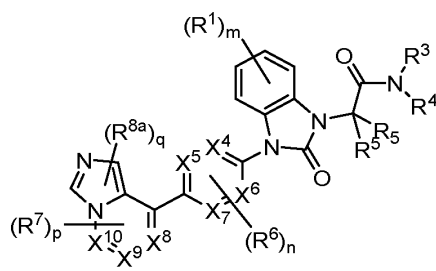
n is an integer selected from 0, 1, 2, 3 and 4;

p is an integer selected from 0, 1, 2 and 3;

q is an integer selected from 0, 1 and 2

wherein any of the aforementioned alkyl, alkylene or cyclopropyl groups is optionally substituted, where chemically possible, by 1 to 5 substituents which are each independently at each occurrence selected from the group consisting of: halo, oxo, fluoro, nitro, cyano, NR^aR^b, OR^a, SR^a, CO₂R^a, C(O)R^a, CONR^aR^a, C₁-C₄-alkyl, C₁-C₄-haloalkyl and cyclopropyl; wherein R^a is independently at each occurrence selected from H, C₁-C₄-alkyl and C₁-C₄-haloalkyl; and R^b is independently at each occurrence selected from H, C₁-C₄-alkyl, C(O)-C₁-C₄-alkyl and S(O)₂-C₁-C₄-alkyl.

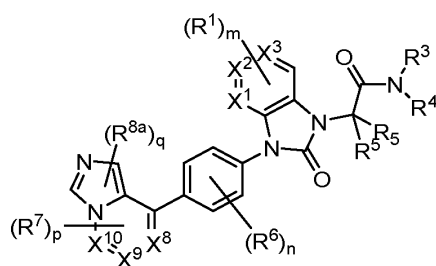
[0010] In an embodiment, the compound of formula (I) or (Ia) is a compound of formula (II):



(II)

wherein X^4 , X^5 , X^6 , X^7 , X^8 , X^9 , X^{10} , R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{8a} , m , n , p and q are as described above for compounds of formula (I) or (Ia).

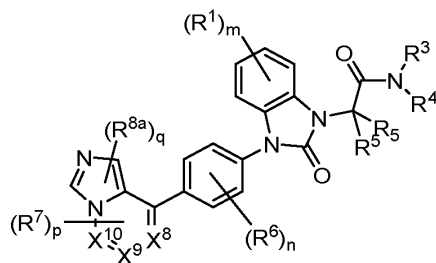
[0011] In an embodiment, the compound of formula (I) or (Ia) is a compound of formula (III):



(III)

wherein X^1 , X^2 , X^3 , X^8 , X^9 , X^{10} , R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{8a} , m , n , p and q are as described above for compounds of formula (I) or (Ia).

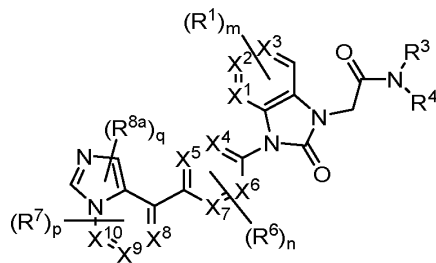
[0012] In an embodiment, the compound of formula (I) or (Ia) is a compound of formula (IV):



(IV)

wherein X^8 , X^9 , X^{10} , R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{8a} , m , n , p and q are as described above for compounds of formula (I) or (Ia).

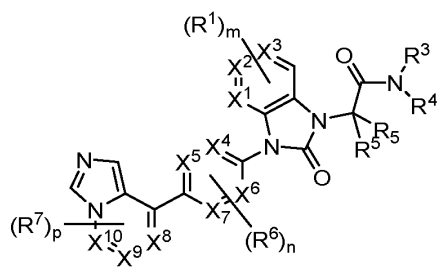
[0013] In an embodiment, the compound of formula (I) or (Ia) is a compound of formula (V):



(V)

wherein X^1 , X^2 , X^3 , X^4 , X^5 , X^6 , X^7 , X^8 , X^9 , X^{10} , R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{8a} , m , n , p and q are as described above for compounds of formula (I) or (Ia).

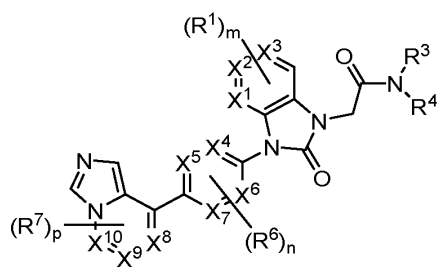
[0014] In an embodiment, the compound of formula (I) or (Ia) is a compound of formula (VI):



(VI)

wherein X^1 , X^2 , X^3 , X^4 , X^5 , X^6 , X^7 , X^8 , X^9 , X^{10} , R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , m , n and p are as described above for compounds of formula (I) or (Ia).

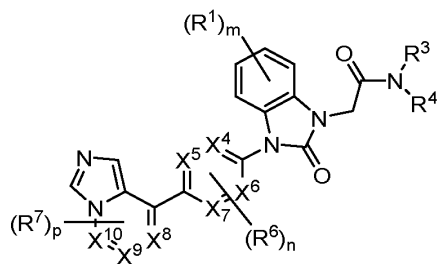
- 5 [0015] In an embodiment, the compound of formula (I) or (Ia) is a compound of formula (VII):



(VII)

wherein X^1 , X^2 , X^3 , X^4 , X^5 , X^6 , X^7 , X^8 , X^9 , X^{10} , R^1 , R^3 , R^4 , R^6 , R^7 , m , n and p are as described above for compounds of formula (I) or (Ia).

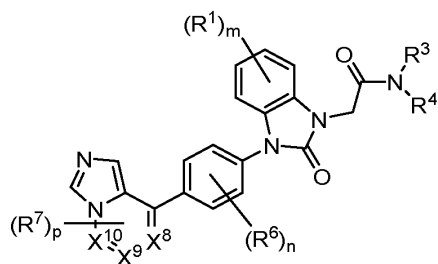
- 10 [0016] In an embodiment, the compound of formula (I) or (Ia) is a compound of formula (VIII):



(VIII)

wherein X^4 , X^5 , X^6 , X^7 , X^8 , X^9 , X^{10} , R^1 , R^3 , R^4 , R^6 , R^7 , m , n and p are as described above for compounds of formula (I) or (Ia).

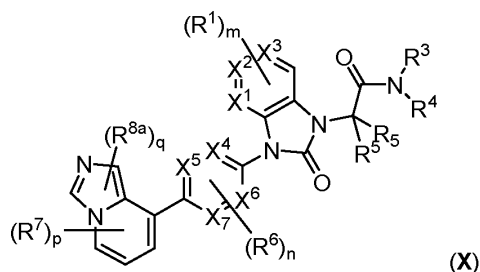
- 15 [0017] In an embodiment, the compound of formula (I) or (Ia) is a compound of formula (IX):



(IX)

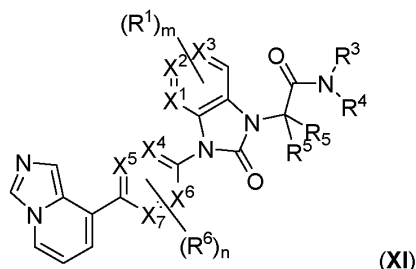
wherein X^8 , X^9 , X^{10} , R^1 , R^3 , R^4 , R^6 , R^7 , m , n and p are as described above for compounds of formula (I) or (Ia).

[0018] In an embodiment, the compound of formula (I) or (Ia) is a compound of formula (X):



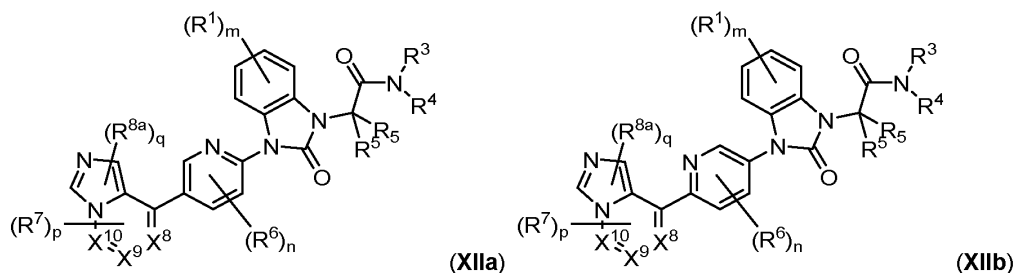
- 5 wherein X^1 , X^2 , X^3 , X^4 , X^5 , X^6 , X^7 , R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{8a} , m , n , p and q are as described above for compounds of formula (I) or (Ia).

[0019] In an embodiment, the compound of formula (I) or (Ia) is a compound of formula (XI):



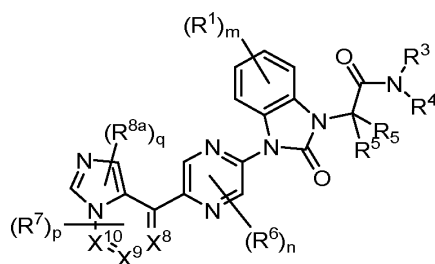
- 10 wherein X^1 , X^2 , X^3 , X^4 , X^5 , X^6 , X^7 , R^1 , R^3 , R^4 , R^5 , R^6 , m and n are as described above for compounds of formula (I) or (Ia).

[0020] In an embodiment, the compound of formula (I) or (Ia) is a compound of formula (XIIa) or (XIIb):

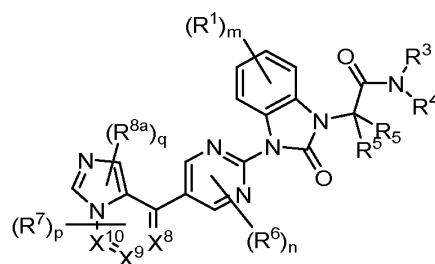


- 15 wherein X^8 , X^9 , X^{10} , R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{8a} , m , n , p and q are as described above for compounds of formula (I) or (Ia).

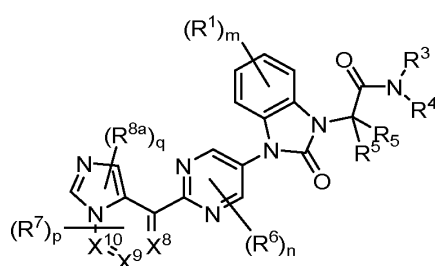
[0021] In an embodiment, the compound of formula (I) or (Ia) is a compound of formula (XIIIa) or (XIIIb) or (XIIIc) or (XIId):



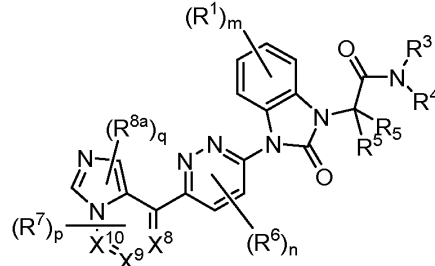
(XIIIa)



(XIIIb)



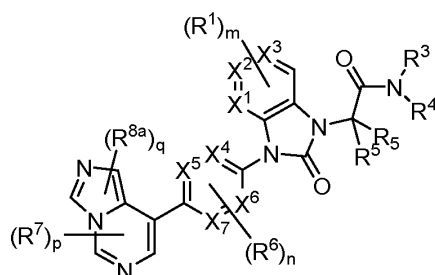
(XIIIc)



(XIIId)

5 wherein X^8 , X^9 , X^{10} , R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{8a} , m , n , p and q are as described above for compounds of formula (I) or (Ia).

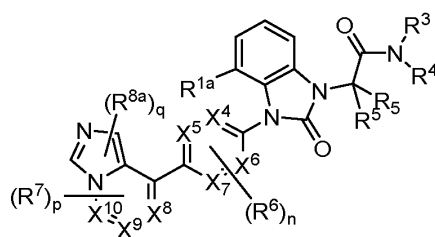
[0022] In an embodiment, the compound of formula (I) or (Ia) is a compound of formula (XIV):



(XIV)

wherein X^1 , X^2 , X^3 , X^4 , X^5 , X^6 , X^7 , R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{8a} , m , n , p and q are as described above for compounds of formula (I) or (Ia).

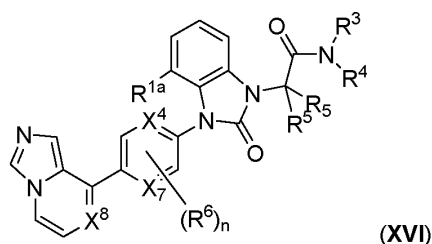
10 **[0023]** In an embodiment, the compound of formula (I) or (Ia) is a compound of formula (XV):



(XV)

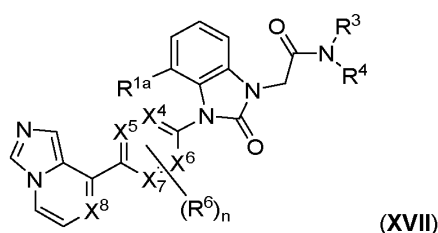
15 wherein X^4 , X^5 , X^6 , X^7 , X^8 , X^9 , X^{10} , R^3 , R^4 , R^5 , R^6 , R^7 , R^{8a} , n , p and q are as described above for compounds of formula (I) or (Ia); and wherein R^{1a} is selected from halo, nitro, cyano, NR^9R^{10} , OR^{11} , SR^9 , $SO_2NR^9R^9$, SO_2R^9 , CO_2R^9 , $C(O)R^9$, $CONR^9R^9$ and C_1 - C_4 -alkyl. R^{1a} may be C_1 - C_4 -alkyl e.g., methyl.

[0024] In an embodiment, the compound of formula (I) is a compound of formula (XVI):



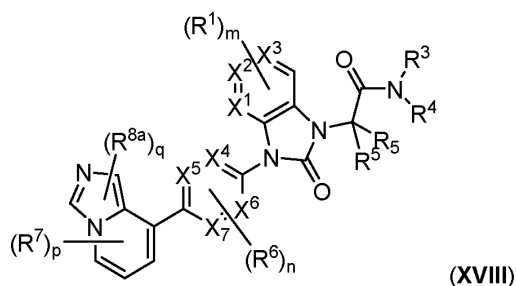
wherein X⁴, X⁷, X⁸, R³, R⁴, R⁵, R⁶, and n are as described above for compounds of formula (I), and wherein R^{1a} is selected from halo, nitro, cyano, NR⁹R¹⁰, OR¹¹, SR⁹, SO₂NR⁹R⁹, SO₂R⁹, CO₂R⁹, C(O)R⁹, CONR⁹R⁹ and C₁-C₄-alkyl. R^{1a} may be C₁-C₄-alkyl e.g., methyl.

- 5 **[0025]** In an embodiment, the compound of formula (I) is a compound of formula (XVII):



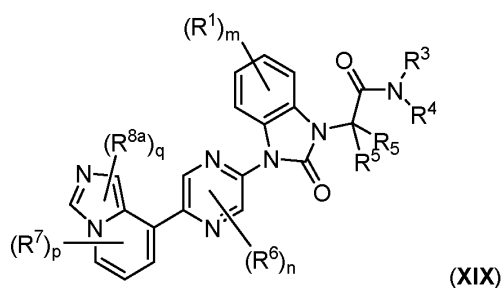
wherein X^4 , X^5 , X^6 , X^7 , X^8 , R^3 , R^4 , R^5 and n are as described above for compounds of formula (I); and wherein R^{1a} is selected from halo, nitro, cyano, NR^9R^{10} , OR^{11} , SR^9 , $SO_2NR^9R^9$, SO_2R^9 , CO_2R^9 , $C(O)R^9$, $CONR^9R^9$ and C_1 - C_4 -alkyl. R^{1a} may be C_1 - C_4 -alkyl e.g., methyl.

- 10 **[0026]** In an embodiment, the compound of formula (I) or (Ia) is a compound of formula (XVIII):



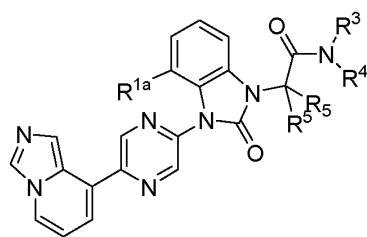
wherein $X^1, X^2, X^3, X^4, X^5, X^6, X^7, R^1, R^3, R^4, R^5, R^6, R^7, R^{8a}, m, n, p$ and q are as described above for compounds of formula (I) or (Ia).

- [0027]** In an embodiment, the compound of formula (I) or (Ia) is a compound of formula (XIX):



wherein R¹, R³, R⁴, R⁵, R⁶, R⁷, R^{8a}, m, n, p and q are as described above for compounds of formula (I) or (Ia).

[0028] In an embodiment, the compound of formula (I) or (Ia) is a compound of formula (XX):



wherein R^3 , R^4 and R^5 are as described above for compounds of formula (I) or (Ia); and wherein R^{1a} is selected from halo, nitro, cyano, NR^9R^{10} , OR^{11} , SR^9 , $SO_2NR^9R^9$, SO_2R^9 , CO_2R^9 , $C(O)R^9$, $CONR^9R^9$ and C_1 - C_4 -alkyl. R^{1a} may be C_1 - C_4 -alkyl e.g., methyl.

[0029] The following embodiments apply to compounds of any of formulae (I)-(XX). These embodiments are independent and interchangeable. Any one embodiment may be combined with any other embodiment, where chemically allowed. In other words, any of the features described in the following embodiments may (where chemically allowable) be combined with the features described in one or more other embodiments. In particular, where a compound is exemplified or illustrated in this specification, any two or more of the embodiments listed below, expressed at any level of generality, which encompass that compound may be combined to provide a further embodiment which forms part of the present disclosure.

[0030] It may be that X^1 is carbon. It may be that X^2 is carbon. It may be that X^3 is carbon. It may be that X^1 and X^2 are both carbon. It may be that X^2 and X^3 are both carbon. It may be that X^1 and X^3 are both carbon. It may be that X^1 , X^2 and X^3 are each carbon.

[0031] It may be that a single one of X^1 , X^2 and X^3 is nitrogen. It may be that X^1 is nitrogen. It may be that X^2 is nitrogen. It may be that X^3 is nitrogen.

[0032] It may be that X^4 is carbon. It may be that X^5 is carbon. It may be that X^6 is carbon. It may be that X^7 is carbon. It may be that X^4 and X^5 are both carbon. It may be that X^4 and X^6 are both carbon. It may be that X^4 and X^7 are both carbon. It may be that X^5 and X^6 are both carbon. It may be that X^5 and X^7 are both carbon. It may be that X^6 and X^7 are both carbon. It may be that X^4 , X^5 and X^6 are each carbon. It may be that X^4 , X^5 and X^7 are each carbon. It may be that X^4 , X^6 and X^7 are each carbon. It may be that X^5 , X^6 and X^7 are each carbon. It may be that X^4 , X^5 , X^6 and X^7 are each carbon.

[0033] It may be that at least one of X^4 , X^5 , X^6 , and X^7 is nitrogen. It may be that a single one of X^4 , X^5 , X^6 , and X^7 is nitrogen. It may be that X^5 is nitrogen. It may be that X^4 is nitrogen. It may be that two of X^4 , X^5 , X^6 , and X^7 are nitrogen. It may be that X^4 and X^5 are each nitrogen. It may be that X^4 and X^7 are each nitrogen. It may be that X^5 and X^7 are each nitrogen. It may be that X^4 and X^6 are each nitrogen.

[0034] It may be that X^4 and X^7 are each nitrogen and X^5 and X^6 are each carbon. It may be that X^5 and X^7 are each nitrogen and X^4 and X^6 are each carbon. It may be that X^5 and X^7 are each carbon and X^4 and X^6 are each nitrogen.

[0035] It may be that X⁸ is carbon. It may be that X⁹ is carbon. It may be that X¹⁰ is carbon. It may be that X⁸ and X⁹ are both carbon. It may be that X⁹ and X¹⁰ are both carbon. It may be that X⁸ and X¹⁰ are both carbon. It may be that X⁸, X⁹ and X¹⁰ are each carbon.

5 [0036] It may be that a single one of X⁸, X⁹ and X¹⁰ is nitrogen. It may be that X⁸ is nitrogen. It may be that X⁹ is nitrogen. It may be that X¹⁰ is nitrogen. It may be that X⁸ is nitrogen and X⁹ and X¹⁰ are each carbon.

[0037] m may be 0. m may be 1. m may be 2. m may be 3. m may be 4.

10 [0038] R¹ may be independently at each occurrence selected from halo, nitro, cyano, OR¹¹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₁-C₄-haloalkyl and cyclopropyl. R¹ may be independently at each occurrence selected from halo, OR¹¹, NR⁹R¹⁰, cyano, C₁-C₄-alkyl and C₁-C₄-haloalkyl. R¹ may be independently at each occurrence selected from halo, OR¹¹, C₁-C₄-alkyl, C₁-C₄-haloalkyl and cyclopropyl. R¹ may be independently at each occurrence selected from halo and C₁-C₄-alkyl. R¹ may be independently at each occurrence halo, e.g. fluoro. R¹ may be independently at each occurrence C₁-C₄-alkyl, e.g. methyl.

15 [0039] It may be that m is at least 1, X¹ is carbon and an R¹ group is attached to the X¹ carbon. It may be that m is 1, X¹ is carbon and the R¹ group is attached to the X¹ carbon.

[0040] R⁵ may be independently at each occurrence selected from H, fluoro and C₁-C₄-alkyl. R⁵ may be independently at each occurrence selected from H, fluoro and C₁-C₄-alkyl, or the two R⁵ groups and the carbon atom to which they are attached may together form a C₃-C₆ cycloalkyl ring. R⁵ may be independently at each occurrence selected from H and C₁-C₄-alkyl, or the two R⁵ groups and the carbon atom to which they are attached may together form a C₃-C₆ cycloalkyl ring. R⁵ may be independently at each occurrence selected from H and C₁-C₄-alkyl, e.g. methyl.

20 [0041] It may be that R⁵ is at each occurrence H. It may be that R⁵ is at one occurrence H and at the other occurrence C₁-C₄-alkyl, e.g. methyl. It may be that R⁵ is at each occurrence C₁-C₄-alkyl, e.g. methyl.

25 [0042] n may be 0. n may be 1. n may be 2. n may be 3. n may be 4.

[0043] R⁶ may be independently selected from halo, nitro, cyano, OR¹¹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₁-C₄-haloalkyl and cyclopropyl. R⁶ may be independently selected from halo, OR¹¹, C₁-C₄-alkyl, C₁-C₄-haloalkyl and cyclopropyl. R⁶ may be independently selected from halo and C₁-C₄-alkyl. R⁶ may be halo, e.g. fluoro. R⁶ may be C₁-C₄-alkyl, e.g. methyl.

30 [0044] p may be 0. p may be 1. p may be 2. p may be 3.

[0045] R⁷ may be independently selected from halo, nitro, cyano, OR¹¹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₁-C₄-haloalkyl and cyclopropyl. R⁷ may be independently selected from halo, OR¹¹, C₁-C₄-alkyl, C₁-C₄-haloalkyl and cyclopropyl. R⁷ may be independently selected from halo and C₁-C₄-alkyl. R⁷ may be halo, e.g. fluoro. R⁷ may be C₁-C₄-alkyl, e.g. methyl.

35 [0046] It may be that q is 0. It may be that q is 1.

- [0047]** R^{8a} may be selected from halo, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₁-C₄-haloalkyl and C₀-C₄-alkylene-R^{8c}. R^{8a} may be selected from halo, C₁-C₄-alkyl, C₁-C₄-haloalkyl and cyclopropyl. R^{8a} may be selected from C₁-C₄-alkyl, C₁-C₄-haloalkyl and cyclopropyl. R^{8a} may be selected from C₁-C₄-alkyl (e.g. methyl) and C₁-C₄-haloalkyl (e.g. CF₃). R^{8a} may be C₁-C₄-alkyl (e.g. methyl). R^{8a} may be halo (e.g. iodo).
- [0048]** R^{8c} is independently selected from C₃-C₈-cycloalkyl and 3- to 7-membered heterocycloalkyl; wherein said heterocycloalkyl group is attached to the C₀-C₄-alkylene via a carbon atom in the heterocycloalkyl ring; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R¹³ groups;
- [0049]** It may be that R⁹ is independently at each occurrence selected from H and C₁-C₄-alkyl.
- [0050]** It may be that R¹⁰ is independently at each occurrence selected from H, C₁-C₄-alkyl, C(O)-C₁-C₄-alkyl and S(O)₂-C₁-C₄-alkyl. It may be that R¹⁰ is independently at each occurrence selected from H and C₁-C₄-alkyl.
- [0051]** It may be that R¹¹ is independently at each occurrence selected from H, C₁-C₄-alkyl and C₁-C₄-haloalkyl. It may be that R¹¹ is independently at each occurrence selected from H and C₁-C₄-alkyl. It may be that R¹¹ is independently at each occurrence C₁-C₄-alkyl, e.g. methyl.
- [0052]** R¹² may be independently selected from 5- or 6- membered heteroaryl, wherein said heteroaryl group is optionally substituted with from 1 to 3 R¹⁴ groups. R¹² may be independently selected from 5- membered heteroaryl, e.g. imidazole, wherein said heteroaryl group is optionally substituted with from 1 to 3 R¹⁴ groups.
- [0053]** R¹³ may be independently at each occurrence selected from oxo, fluoro, OR¹¹, CO₂R⁹, CO₂NR⁹R¹⁰, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₁-C₄-haloalkyl and cyclopropyl. R¹³ may be independently at each occurrence selected from oxo, OR¹¹, C₁-C₄-alkyl and cyclopropyl. R¹³ may be independently at each occurrence selected from oxo and C₁-C₄-alkyl. R¹³ may be independently at each occurrence C₁-C₄-alkyl, e.g. methyl.
- [0054]** R¹⁴ may be independently at each occurrence selected from halo, nitro, cyano, OR¹¹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₁-C₄-haloalkyl and cyclopropyl. R¹⁴ may be independently at each occurrence selected from halo, nitro, cyano, OR¹¹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₁-C₄-haloalkyl and cyclopropyl. R¹⁴ may be independently at each occurrence selected from halo, OR¹¹, C₁-C₄-alkyl, C₁-C₄-haloalkyl and cyclopropyl. R¹⁴ may be independently at each occurrence selected from halo and C₁-C₄-alkyl. R¹⁴ may be independently at each occurrence halo, e.g. fluoro. R¹⁴ may be independently at each occurrence C₁-C₄-alkyl, e.g. methyl.
- [0055]** It may be that:
- R³ is H; and
- R⁴ is independently selected from C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₀-C₄-alkylene-R^{4a}; wherein R^{4a} is independently selected from: C₃-C₈-cycloalkyl, phenyl, 5-, 6-, 9- or 10-membered heteroaryl and 4- to 10-membered heterocycloalkyl; wherein said heterocycloalkyl or heteroaryl group may be monocyclic or bicyclic; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with a single R¹²

group and/or from 1 to 4 R^{13} groups and wherein said phenyl or heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups;

or R^3 and R^4 , together with the nitrogen atom to which they are attached together form a 4- to 10-membered heterocycloalkyl group or a 5-, or 9-membered heteroaryl group; wherein said

- 5 heterocycloalkyl group is optionally substituted with a single R^{12} group and/or from 1 to 4 R^{13} groups and wherein said heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups.

[0056] It may be that:

R^3 is H; and

- 10 R^4 is independently selected from C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_0 - C_4 -alkylene- R^{4a} ; wherein R^{4a} is independently selected from: C_3 - C_8 -cycloalkyl, phenyl, 5-, 6-, 9- or 10-membered heteroaryl and 4- to 10-membered heterocycloalkyl; wherein said heterocycloalkyl or heteroaryl group may be monocyclic or bicyclic; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R^{13} groups and wherein said phenyl or heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups;

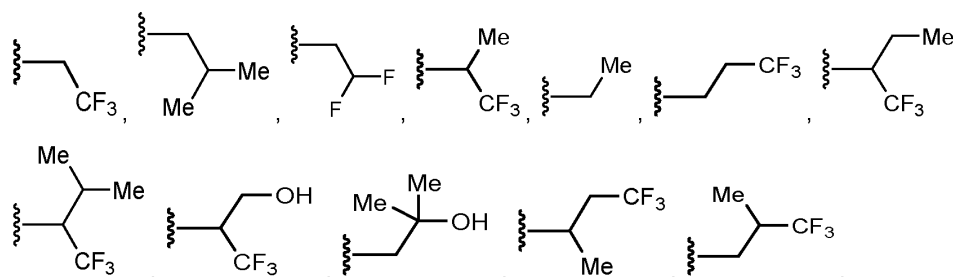
or R^3 and R^4 , together with the nitrogen atom to which they are attached together form a 4- to 10-membered heterocycloalkyl group or a 5-, or 9-membered heteroaryl group; wherein said heterocycloalkyl group is optionally substituted with from 1 to 4 R^{13} groups and wherein said heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups.

- 20 **[0057]** It may be that R^3 is H.

[0058] It may be that R^4 is selected from C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl and C_0 - C_4 -alkylene- R^{4a} .

[0059] It may be that R^4 is selected from C_1 - C_6 -alkyl and C_1 - C_6 -haloalkyl. It may be that R^4 is selected from C_2 - C_3 -alkyl and C_2 - C_3 -haloalkyl. It may be that R^4 is C_1 - C_4 -haloalkyl. It may be that R^4 is C_2 - C_3 -haloalkyl. It may be that R^4 is 2,2,2-trifluoroethyl.

- 25 **[0060]** Illustrative R^4 groups include:



[0061] It may be that R^4 is C_0 - C_4 -alkylene- R^{4a} . It may be that R^4 is CH_2 - R^{4a} . It may be that R^4 is R^{4a} .

- 30 **[0062]** It may be that R^{4a} is independently selected from C_3 - C_8 -cycloalkyl, phenyl, 5-, 6-, 9- or 10-membered heteroaryl, 4- to 10-membered heterocycloalkyl, wherein said heterocycloalkyl or heteroaryl group may be monocyclic or bicyclic; wherein said cycloalkyl or heterocycloalkyl group is

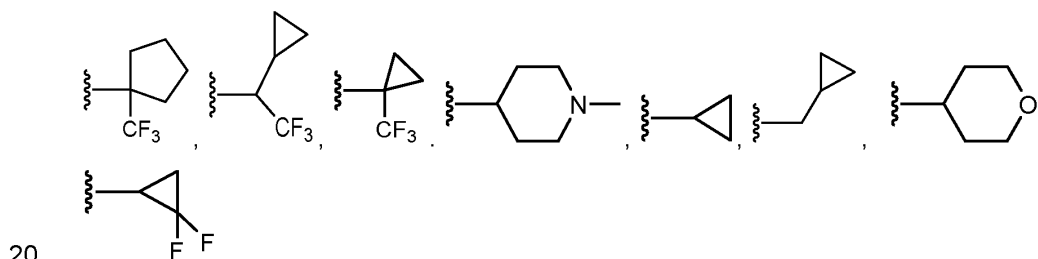
optionally substituted with from 1 to 4 R^{13} groups and wherein said phenyl or heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups.

[0063] It may be that R^{4a} is selected from C_3 - C_8 -cycloalkyl and 4- to 10-membered heterocycloalkyl, wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with a single R^{12} group and/or from 1 to 4 R^{13} groups. It may be that R^{4a} is selected from C_3 - C_8 -cycloalkyl and 4- to 10-membered heterocycloalkyl, wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R^{13} groups.

[0064] It may be that R^4 is selected from CH_2 - C_3 - C_8 -cycloalkyl and CH_2 -4- to 10-membered heterocycloalkyl, wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with a single R^{12} group and/or from 1 to 4 R^{13} groups. It may be that R^4 is selected from CH_2 - C_3 - C_8 -cycloalkyl and CH_2 -4- to 10-membered heterocycloalkyl, wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R^{13} groups.

[0065] It may be that R^4 is selected from C_3 - C_8 -cycloalkyl and 4- to 10-membered heterocycloalkyl, wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with a single R^{12} group and/or from 1 to 4 R^{13} groups. It may be that R^4 is selected from C_3 - C_8 -cycloalkyl and 4- to 10-membered heterocycloalkyl, wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R^{13} groups.

[0066] Illustrative R^4 groups include:



[0067] It may be that R^{4a} is independently selected from: phenyl and 5- or 6- membered heteroaryl; wherein said phenyl or heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^{4a} is independently selected from: phenyl and 5- or 6- membered heteroaryl; wherein said phenyl or heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups. It may be that R^{4a} is independently phenyl; wherein said phenyl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^{4a} is independently phenyl; wherein said phenyl group is optionally substituted with from 1 to 3 R^{14} groups. It may be that R^{4a} is independently 5- or 6- membered heteroaryl; wherein said heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^{4a} is independently 5- or 6- membered heteroaryl; wherein said heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups.

[0068] It may be that R^4 is independently selected from CH_2 -phenyl or CH_2 -5- or 6- membered heteroaryl wherein said phenyl or heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^4 is independently selected from CH_2 -phenyl or CH_2 -5- or 6- membered heteroaryl wherein said phenyl or heteroaryl group is optionally substituted with from

1 to 3 R^{14} groups. It may be that R^4 is independently CH_2 -phenyl wherein said phenyl is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^4 is independently CH_2 -phenyl wherein said phenyl group is optionally substituted with from 1 to 3 R^{14} groups. It may be that R^4 is independently CH_2 -5- or 6- membered heteroaryl wherein said heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^4 is independently CH_2 -5- or 6- membered heteroaryl wherein said heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups.

[0069] It may be that R^4 is independently selected from phenyl or 5- or 6- membered heteroaryl wherein said phenyl or heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^4 is independently selected from phenyl or 5- or 6- membered heteroaryl wherein said phenyl or heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups. It may be that R^4 is independently phenyl wherein said phenyl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^4 is independently phenyl wherein said phenyl group is optionally substituted with from 1 to 3 R^{14} groups. It may be that R^4 is independently 5- or 6- membered heteroaryl wherein said heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^4 is independently 5- or 6- membered heteroaryl wherein said heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups.

[0070] It may be that R^4 is independently selected from phenyl or 6-membered heteroaryl wherein said phenyl or 6-membered heteroaryl group is substituted at the meta position with 1 R^{14} group. It may be that the R^{14} group is selected from C_1 - C_4 -alkyl substituted with OR^{11} , C_1 - C_4 -alkyl and C_1 - C_4 -haloalkyl. It may be that the R^{14} group at the meta position is C_1 - C_4 -alkyl substituted with OR^{11} e.g. $-(CH_3)_2-OH$. It may be that the R^{14} group at the meta position is C_1 - C_4 -haloalkyl e.g. CF_3 .

[0071] It may be that R^4 is a 6-membered heteroaryl group. It may be that R^4 is phenyl. It may be that R^4 is phenyl substituted at the meta position with 1 R^{14} group. It may be that R^{14} is R^{14a} . Illustrative R^4 groups include:



wherein R^{14a} is selected from halo, nitro, cyano, NR^8R^9 , OR^{10} , SR^8 , SO_2R^8 , $SO_2NR^8R^8$, CO_2R^8 , $C(O)R^8$, $CONR^8R^8$, C_1 - C_4 -alkyl, C_2 - C_4 -alkenyl, C_2 - C_4 -alkynyl, C_1 - C_4 -haloalkyl, C_1 - C_4 -alkyl substituted with OR^{11} , C_1 - C_4 -alkyl substituted with NR^8R^9 and cyclopropyl; and wherein z is an integer selected from 1 and 2.

[0072] It may be that R^4 is a 6-membered heteroaryl group. It may be that R^4 is phenyl. It may be that R^4 is phenyl substituted at the meta position with 1 R^{14} group. It may be that R^{14} is R^{14a} . Illustrative R^4 groups include:

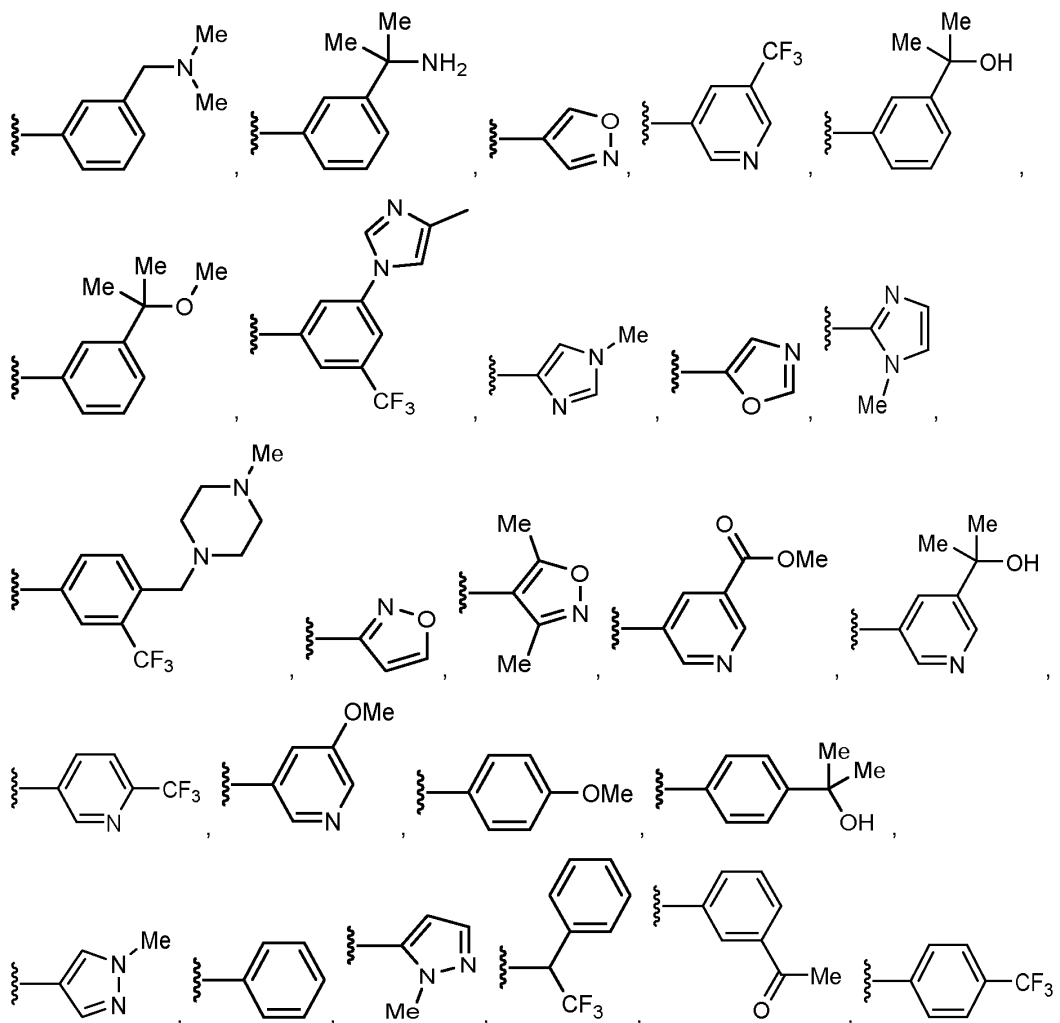
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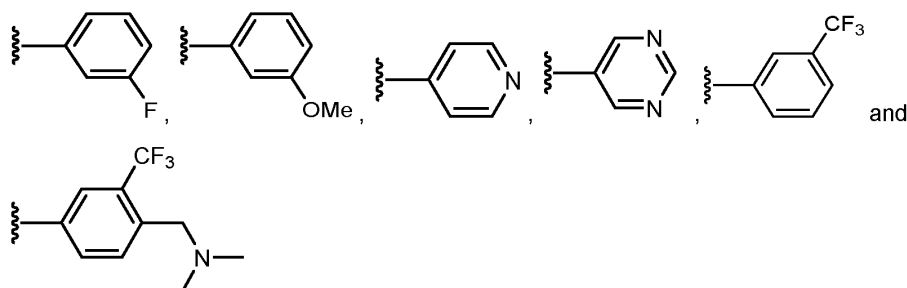
wherein R^{14a} is selected from halo, nitro, cyano, NR^9R^{10} , OR^{11} , SR^9 , SO_2R^9 , $SO_2NR^9R^9$, CO_2R^9 , $C(O)R^9$, $CONR^9R^9$, C_1 - C_4 -alkyl, C_2 - C_4 -alkenyl, C_2 - C_4 -alkynyl, C_1 - C_4 -haloalkyl, C_1 - C_4 -alkyl substituted with OR^{11} , C_1 - C_4 -alkyl substituted with NR^9R^{10} and cyclopropyl; and wherein z is an integer selected from 1 and 2.

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[0073] Illustrative R^4 groups include:



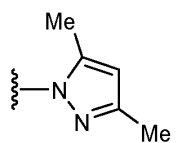
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[0074] It may be that R^3 and R^4 , together with the nitrogen atom to which they are attached together form a 4- to 10-membered heterocycloalkyl group or a 5-, or 9-membered heteroaryl group; wherein said heterocycloalkyl group is optionally substituted with a single R^{12} group and/or from 1 to 4 R^{13} groups and wherein said heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^3 and R^4 , together with the nitrogen atom to which they are attached together form a 4- to 10-membered heterocycloalkyl group or a 5-, or 9- membered heteroaryl group; wherein said heterocycloalkyl group is optionally substituted with from 1 to 4 R^{13} groups and wherein said heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups.

[0075] It may be that R^3 and R^4 , together with the nitrogen atom to which they are attached together form a 5-, or 9-membered heteroaryl group; wherein heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^3 and R^4 , together with the nitrogen atom to which they are attached together form a 5-, or 9-membered heteroaryl group; wherein said heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups. It may be that R^3 and R^4 , together with the nitrogen atom to which they are attached together form a 5- membered heteroaryl group; wherein heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^3 and R^4 , together with the nitrogen atom to which they are attached together form a 5-membered heteroaryl group; wherein said heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups.

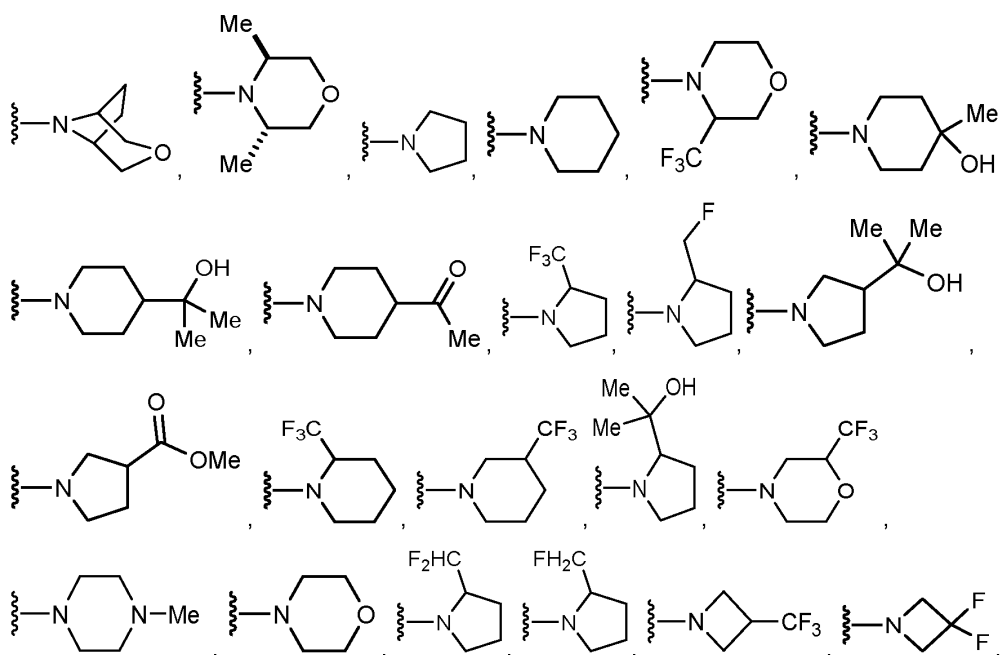
[0076] Illustrative NR^3R^4 groups include:



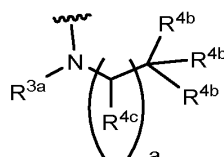
[0077] It may be that R^3 and R^4 , together with the nitrogen atom to which they are attached together form a 4- to 10-membered heterocycloalkyl group; wherein said heterocycloalkyl group is optionally substituted with a single R^{12} group and/or from 1 to 4 R^{13} groups. It may be that R^3 and R^4 , together with the nitrogen atom to which they are attached together form a 4- to 10-membered heterocycloalkyl group; wherein said heterocycloalkyl group is optionally substituted with from 1 to 4 R^{13} groups. It may be that said heterocycloalkyl group is 7- to 10-membered bicyclic heterocycloalkyl group. It may be that said heterocyclic group is 7- to 10-membered bridged bicyclic heterocycloalkyl group. It may be that said heterocyclic group is a monocyclic 4- to 7- membered heterocycloalkyl group. It may be that said heterocyclic group is a monocyclic 5- to 6- membered heterocycloalkyl group. It may be that said

- heterocyclic group is pyrrolidine. It may be that said heterocyclic group is piperidine. It may be that said heterocyclic group is morpholine. It may be that said heterocyclic group is piperazine. For the absence of doubt the heterocycloalkyl groups mentioned in this paragraph are optionally substituted with a single R^{12} group and/or from 1 to 4 R^{13} groups. It may be that the heterocycloalkyl groups mentioned in this paragraph are optionally substituted with from 1 to 4 R^{13} groups. It may be that said heterocyclic group is pyrrolidine and is substituted at the 2 position with 1 R^{13} group. It may be that said heterocyclic group is pyrrolidine and is substituted at the 3 position with 1 R^{13} group. It may be that said heterocyclic group is piperidine and is substituted at the 2 position with 1 R^{13} group. It may be that said heterocyclic group is piperidine and is substituted at the 3 position with 1 R^{13} group. It may be that said heterocyclic group is piperidine and is substituted at the 4 position with 1 R^{13} group. It may be that said heterocyclic group is morpholine and is substituted at the 2 position with 1 R^{13} group. It may be that said heterocyclic group is morpholine and is substituted at the 3 position with 1 R^{13} group.. It may be that the R^{13} group is selected from C_1 - C_4 -alkyl, C_1 - C_4 -alkyl substituted with OR^{11} e.g. $-(CH_3)_2-OH$, and C_1 - C_4 -haloalkyl, e.g. $-CF_3$.

- 15 [0078] Illustrative NR^3R^4 groups include:



- 20 [0079] It may be that R^3 and R^4 are selected such that NR^3R^4 comprises a CHF_2 group or a CF_3 group.



- [0080] It may be that NR^3R^4 has the formula $\text{N}(\text{R}^{3a})\text{C}(\text{R}^{4c})\text{C}(\text{R}^{4b})_2$; wherein a is an integer selected from 1 and 2;

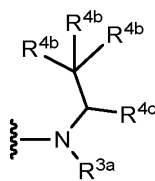
R^{4b} is at each occurrence selected from H and F; wherein at least one R^{4b} group is F;

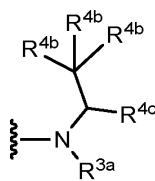
R^{3a} is independently selected from H and C₁-C₄-alkyl;

R^{4c} is independently at each occurrence selected from H, C₁-C₄-alkyl and C₄-C₆-cycloalkyl; or

R^{3a} and a single R^{4c} , together with the carbon and nitrogen to which they are attached, form a 4- to 6-membered heterocycloalkyl group.

- 5 **[0081]** a may be 1. a may be 2.



[0082] It may be that $NR^{3a}R^{4c}$ has the formula ; wherein

R^{4b} is at each occurrence selected from H and F; wherein at least one R^{4b} group is F;

R^{3a} is independently selected from H and C₁-C₄-alkyl;

R^{4c} is independently selected from H, C₁-C₄-alkyl and C₄-C₆-cycloalkyl; or

- 10 R^{3a} and R^{4c} , together with the carbon and nitrogen to which they are attached, form a 4- to 6-membered heterocycloalkyl group.

[0083] It may be that at least two R^{4b} groups are F. It may be that two R^{4b} groups are F and one R^{4b} group is H. It may be that each R^{4b} group is F.

[0084] It may be that R^{3a} is H.

- 15 **[0085]** It may be that R^{3a} is independently selected from H and C₁-C₄-alkyl; and R^{4c} is independently selected from H, C₁-C₄-alkyl and C₄-C₆-cycloalkyl. It may be that R^{3a} is H; and R^{4c} is independently selected from H, C₁-C₄-alkyl and C₄-C₆-cycloalkyl. Said alkyl or cycloalkyl group may be unsubstituted.

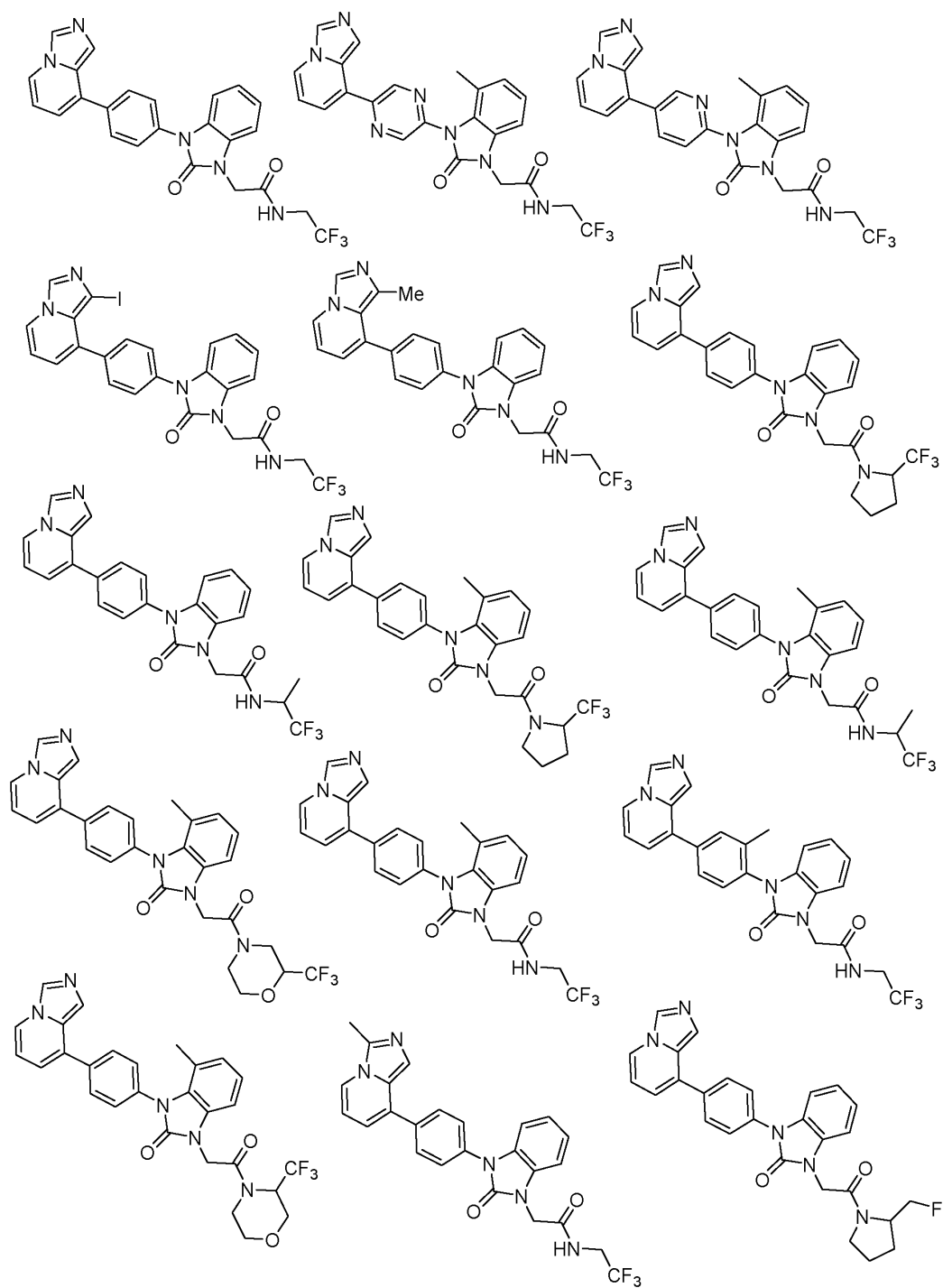
[0086] It may be that R^{4c} is at each occurrence selected from C₁-C₄-alkyl (e.g. methyl) and H. It

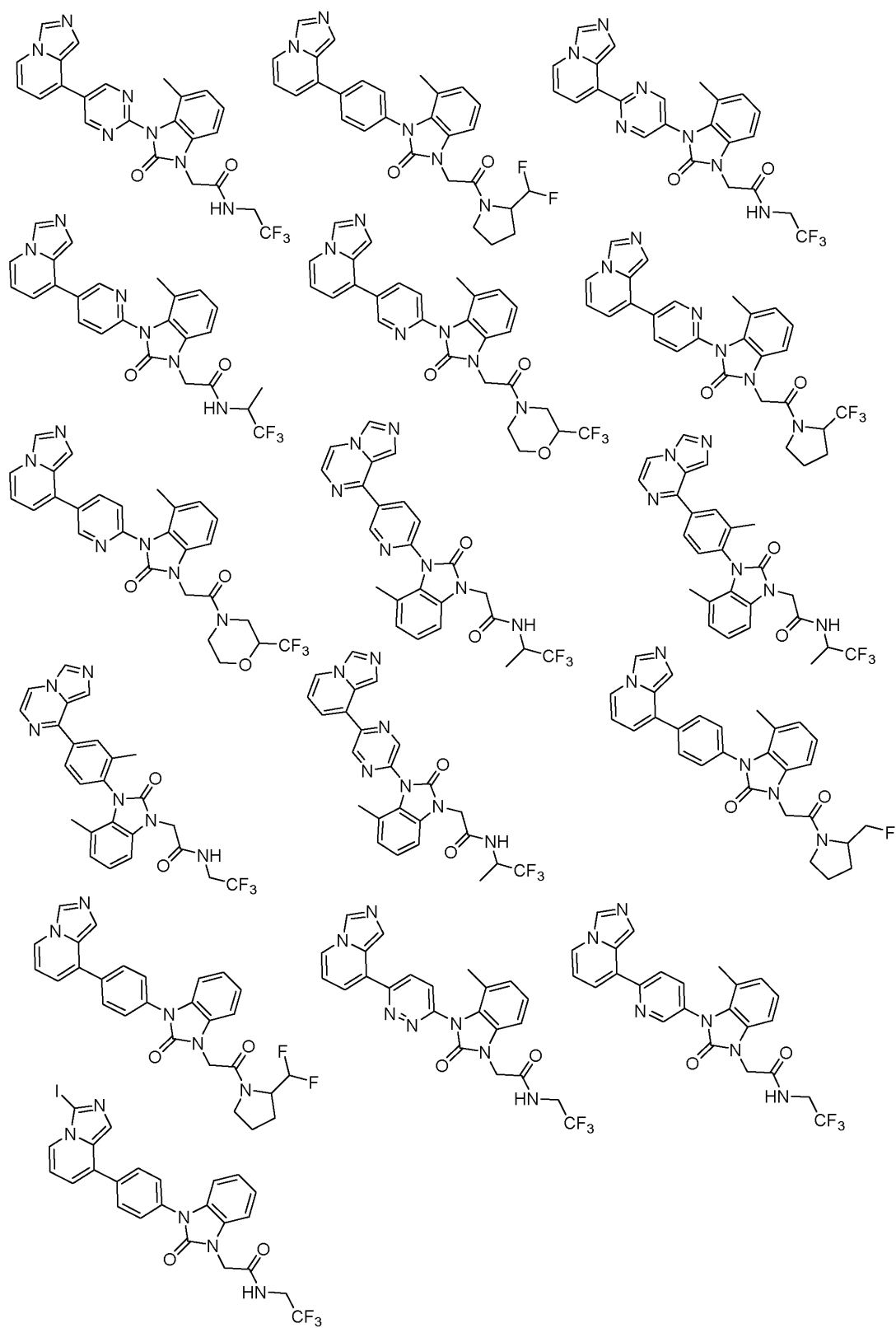
- 20 may be that R^{4c} is at each occurrence H.

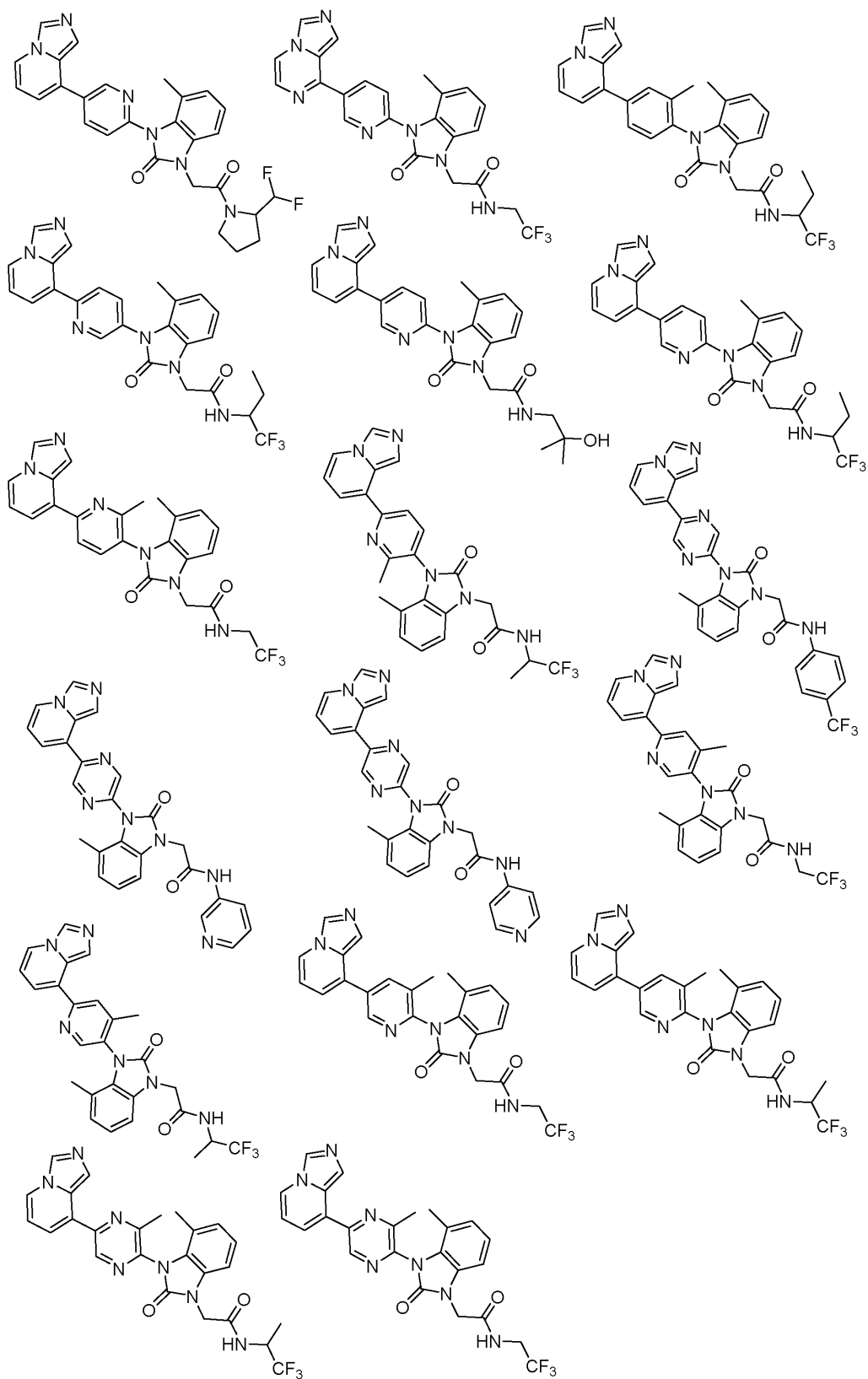
[0087] It may be that R^{3a} and R^{4c} , together with the carbon and nitrogen to which they are attached, form a 4- to 6-membered heterocycloalkyl group. It may be that R^{3a} and R^{4c} , together with the carbon and nitrogen to which they are attached, form a 5-membered heterocycloalkyl group. It may be that R^{3a} and R^{4c} , together with the carbon and nitrogen to which they are attached, form a 6-membered

- 25 heterocycloalkyl group. Said heterocycloalkyl group might be unsubstituted.

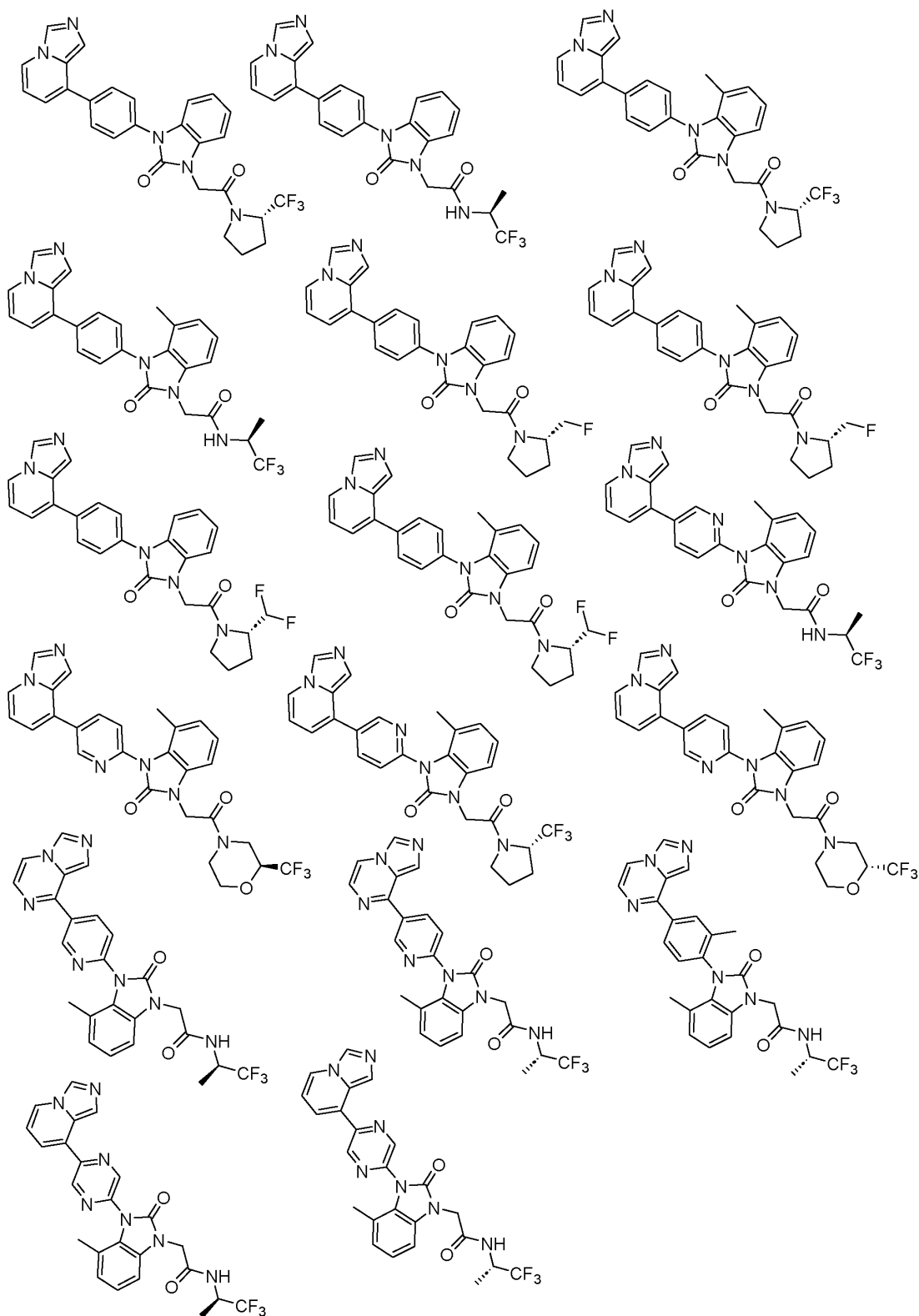
[0088] The compound of formula (I) may be selected from:

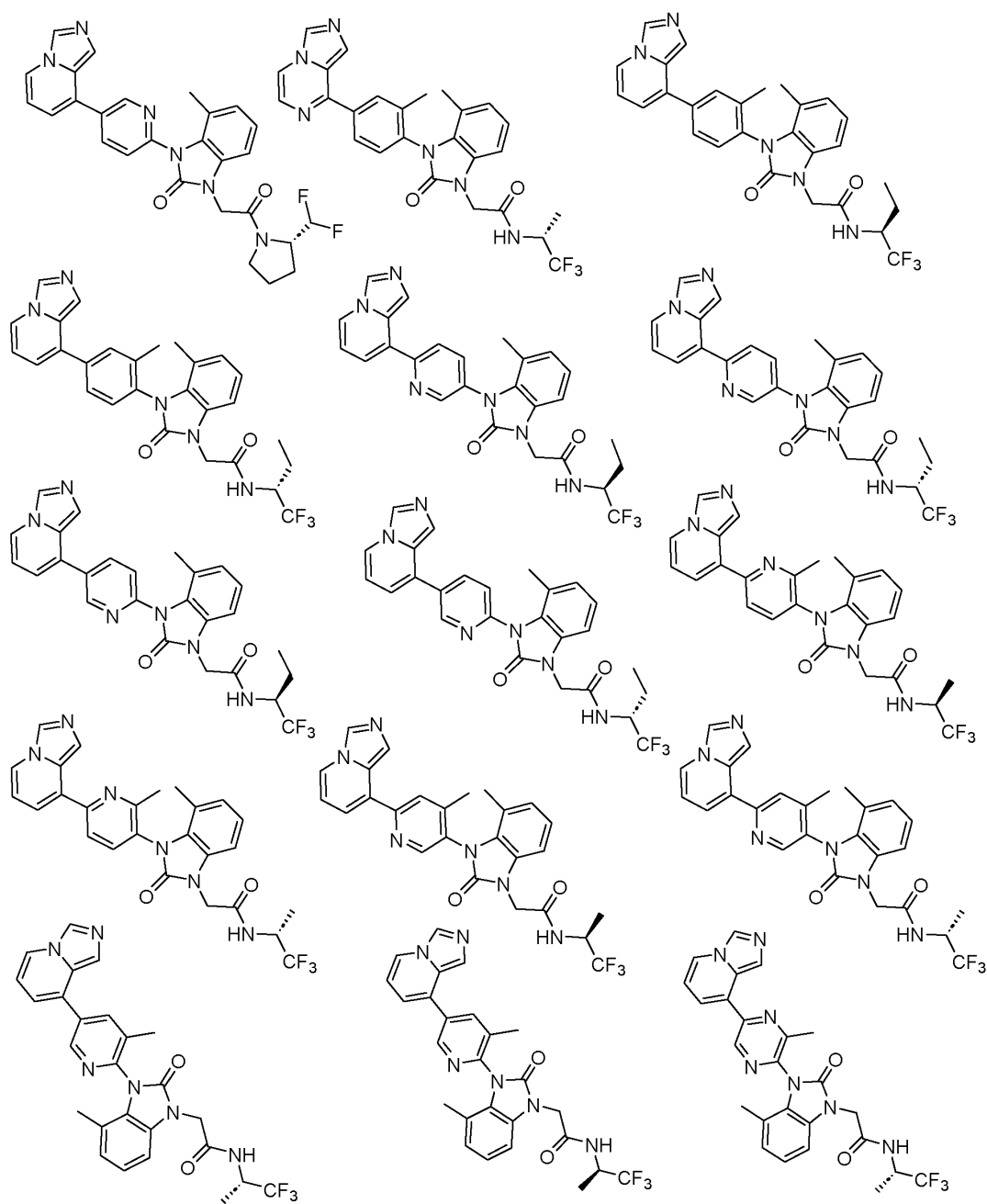


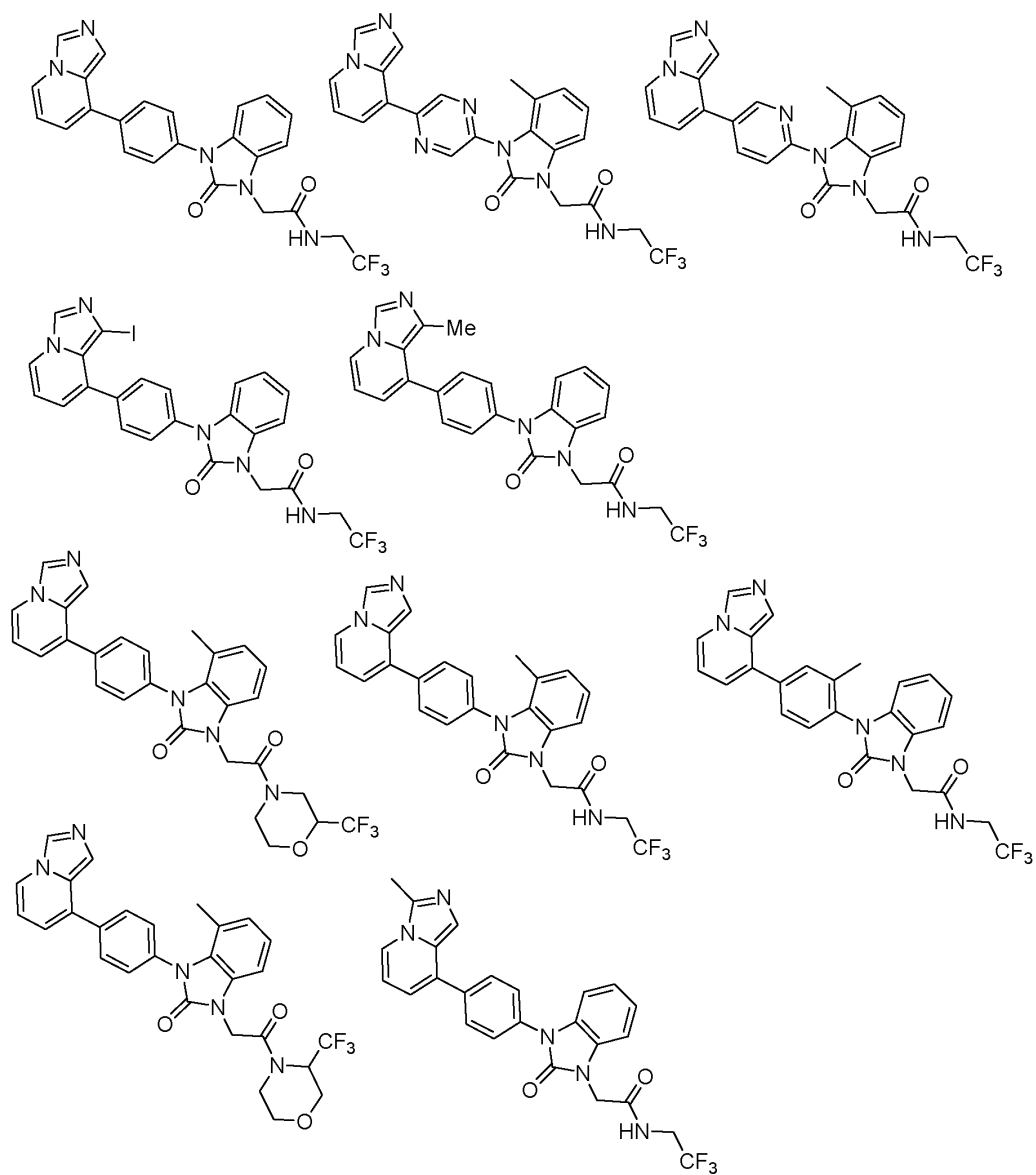


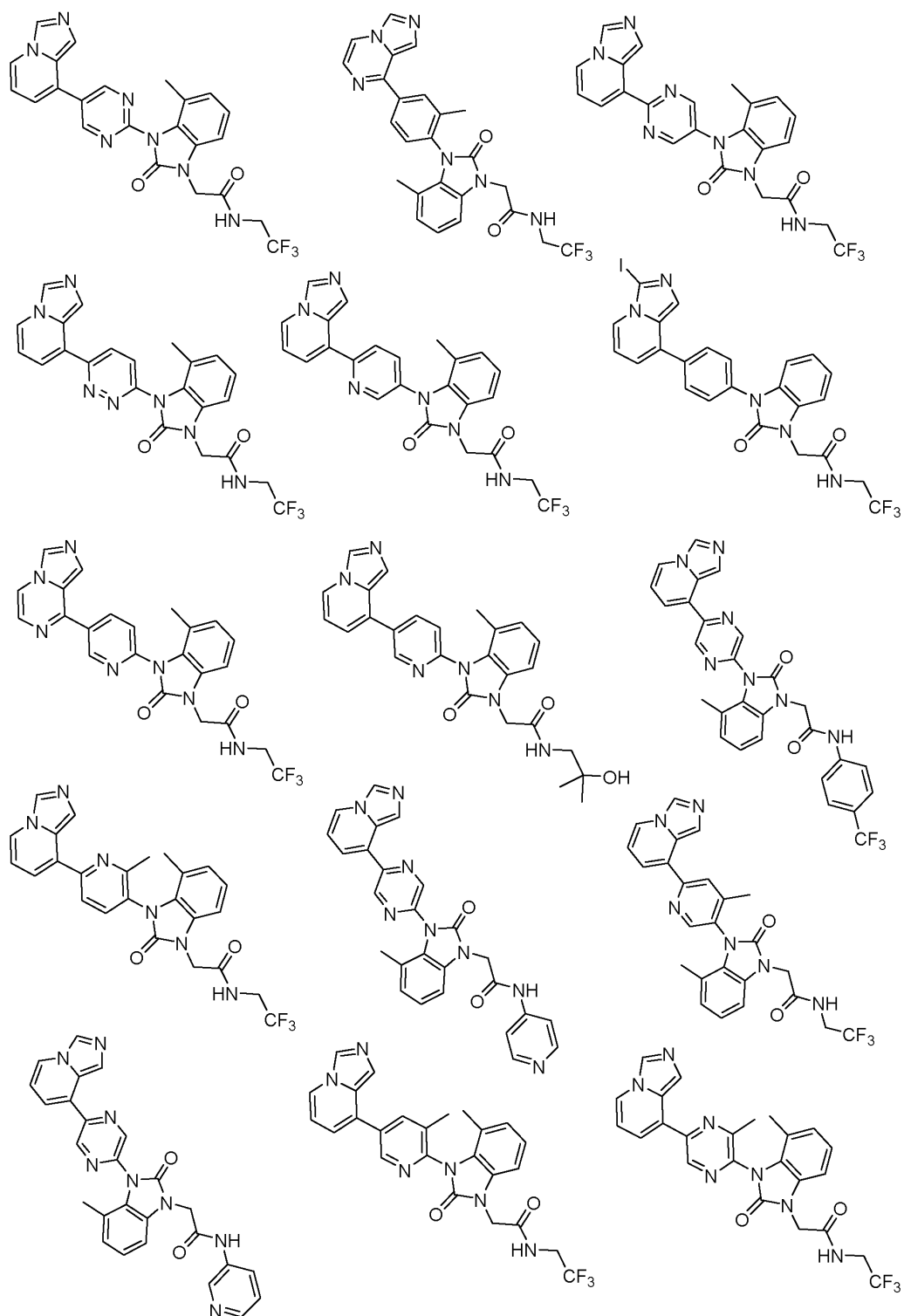


[0089] The compound of formula (I) may be selected from:









[0090] In an aspect of the invention there is provided the compounds of the present invention for use as a medicament.

[0091] In accordance with another aspect, there is provided a compound of the present invention for use in the treatment of a condition which is modulated by DDR1 and/or DDR2. A compound of any formula disclosed herein may be for use in the treatment of a condition treatable by the inhibition of DDR1 and/or DDR2.

- 5 **[0092]** In another aspect of the invention, there is provided a compound of the present invention for use in the treatment of a disease or disorder selected from: renal conditions, liver conditions, inflammatory conditions, cardiovascular conditions, acute and chronic organ transplant rejection, fibrotic diseases and cancer.,

- 10 **[0093]** In an aspect of the invention there is provided a method of treating a disease or disorder which is modulated by DDR1 and/or DDR2 wherein the method comprises administering a therapeutic amount of a compound of the invention, to a patient in need thereof.

[0094] The method of treatment may be a method of treating a condition treatable by the inhibition of DDR1 and/or DDR2.

- 15 **[0095]** The invention also provides a method of treating a disease or disorder selected from: renal conditions, liver conditions, inflammatory conditions, cardiovascular conditions, acute and chronic organ transplant rejection, fibrotic diseases and cancer wherein the method comprises administering a therapeutic amount of a compound of any formula disclosed herein, to a patient in need thereof.

- 20 **[0096]** Renal conditions include, acute kidney injury and chronic renal disease with and without proteinuria including end-stage renal disease (ESRD). This includes decreased creatinine clearance and decreased glomerular filtration rate, micro albuminuria, albuminuria and proteinuria, glomerulosclerosis with expansion of reticulated mesangial matrix with or without significant hypercellularity (particularly diabetic nephropathy and amyloidosis), focal thrombosis of glomerular capillaries (particularly thrombotic microangiopathies), global fibrinoid necrosis, ischemic lesions, malignant nephrosclerosis (such as ischemic retraction, reduced renal blood flow and renal
- 25 arteriopathy), swelling and proliferation of intracapillary (endothelial and mesangial) and/or extracapillary cells (crescents) like in glomerular nephritis entities, focal segmental glomerular sclerosis, IgA nephropathy, vasculitis / systemic diseases as well as acute and chronic kidney transplant rejection. Early and advanced Alport syndrome are also included amongst renal conditions.

- 30 **[0097]** Inflammatory conditions include, arthritis, osteoarthritis, multiple sclerosis, systemic lupus erythematoses, inflammatory bowel disease, abnormal evacuation disorder and the like as well as inflammatory airways diseases such as idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD) or chronic asthma. Further conditions of the respiratory system include other diffuse parenchymal lung diseases of different etiologies including iatrogenic drug-induced fibrosis, occupational and/or environmental induced fibrosis, systemic diseases and vasculitis,
- 35 granulomatous diseases (sarcoidosis, hypersensitivity pneumonia), collagen vascular disease, radiation induced fibrosis.

[0098] Vascular conditions include atherosclerosis, thrombotic vascular disease as well as thrombotic microangiopathies, proliferative arteriopathy (such as swollen myointimal cells surrounded by mucinous extracellular matrix and nodular thickening), atherosclerosis, decreased vascular

compliance (such as stiffness, reduced ventricular compliance and reduced vascular compliance), endothelial dysfunction and the like.

[0099] Cardiovascular conditions include acute coronary syndrome, coronary heart disease, myocardial infarction, arterial and pulmonary hypertension, cardiac arrhythmia such as atrial fibrillation, stroke and other vascular damage.

[00100] Fibrotic diseases include, but are not limited to myocardial and vascular fibrosis, renal fibrosis, liver fibrosis, pulmonary fibrosis, skin fibrosis, scleroderma and encapsulating peritonitis, systemic sclerosis, Alport syndrome, Chronic kidney disease, NASH, Interstitial lung diseases and Systemic Sclerosis.

[00101] In certain embodiments compounds of the invention are for use in the treatment of or are used in a method of treatment of cancer. Examples include but are not limited to: liver cancer, bladder cancer, hepatoma, squamous carcinoma of the lung, non-small cell lung cancer, adenocarcinoma of the lung, small-cell lung cancer, various types of head and neck cancer, breast cancer, colon cancer, colorectal cancer, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, esophageal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, squamous cell cancer, pituitary cancer, astrocytoma, soft tissue sarcoma, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, brain cancer, endometrial cancer, testis cancer, cholangiocarcinoma, gallbladder carcinoma, gastric cancer and melanoma. In certain embodiments, the cancer is selected from bladder cancer, pancreatic cancer, breast cancer, lung cancer, ovarian cancer and glioblastoma.

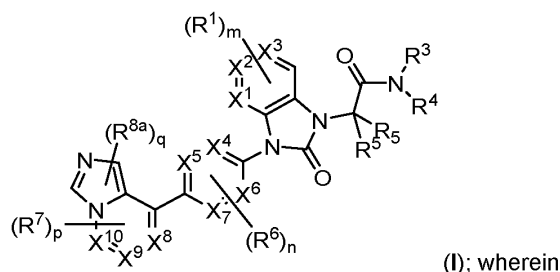
[00102] In another aspect of the invention there is provided a pharmaceutical composition, wherein the composition comprises a compound of the invention and pharmaceutically acceptable excipients.

[00103] In an embodiment the pharmaceutical composition may be a combination product comprising an additional pharmaceutically active agent.

[00104] In an aspect of the present invention there is provided the use of a compound of the invention in the manufacture of a medicament for use in the treatment of any condition disclosed herein.

[00105] The invention may be defined according to the following numbered clauses:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:

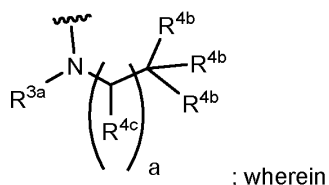


X¹, X² and X³ are each independently selected from carbon and nitrogen, wherein at least two of X¹, X² and X³ are carbon;

- X^4 , X^5 , X^6 and X^7 are each independently selected from carbon and nitrogen, wherein at least two of X^4 , X^5 , X^6 and X^7 are carbon;
- X^8 , X^9 and X^{10} are each independently selected from carbon and nitrogen, wherein at least two of X^8 , X^9 and X^{10} are carbon;
- 5 R^1 is independently selected at each occurrence from halo, nitro, cyano, NR^9R^{10} , OR^{11} , SR^9 , $SO_2NR^9R^9$, SO_2R^9 , CO_2R^9 , $C(O)R^9$, $CONR^9R^9$, C_1 - C_4 -alkyl, C_1 - C_4 -alkyl substituted with NR^9R^{10} , C_1 - C_4 -alkyl substituted with OR^{11} , C_2 - C_4 -alkenyl, C_2 - C_4 -alkynyl, C_1 - C_4 -haloalkyl and cyclopropyl;
 R^3 is independently selected from H and C_1 - C_4 -alkyl;
 R^4 is independently selected from C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_0 - C_4 -alkylene- R^{4a} ; wherein R^{4a} is
- 10 independently selected from: C_3 - C_8 -cycloalkyl, phenyl, 5-, 6-, 9- or 10-membered heteroaryl and 4- to 10-membered heterocycloalkyl; wherein said heterocycloalkyl or heteroaryl group may be monocyclic or bicyclic; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with a single R^{12} group and/or from 1 to 4 R^{13} groups and wherein said phenyl or heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups;
- 15 or R^3 and R^4 , together with the nitrogen atom to which they are attached together form a 4- to 10-membered heterocycloalkyl group or a 5-, or 9-membered heteroaryl group; wherein said heterocycloalkyl or heteroaryl group may be monocyclic or bicyclic; wherein said heterocycloalkyl group is optionally substituted with a single R^{12} group and/or from 1 to 4 R^{13} groups and wherein said heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups;
- 20 R^5 is independently at each occurrence selected from H, halo and C_1 - C_4 -alkyl, or the two R^5 groups and the carbon atom to which they are attached may together form a C_3 - C_6 cycloalkyl ring;
 R^6 is independently at each occurrence selected from halo, nitro, cyano, NR^9R^{10} , OR^{11} , SR^9 , $SO_2NR^9R^9$, SO_2R^9 , CO_2R^9 , $C(O)R^9$, $CONR^9R^9$, C_1 - C_4 -alkyl, C_1 - C_4 -alkyl substituted with NR^9R^{10} , C_1 - C_4 -alkyl substituted with OR^{11} , C_2 - C_4 -alkenyl, C_2 - C_4 -alkynyl, C_1 - C_4 -haloalkyl and cyclopropyl;
- 25 R^7 is independently at each occurrence selected from halo, nitro, cyano, NR^9R^{10} , OR^{11} , SR^9 , $SO_2NR^9R^9$, SO_2R^9 , CO_2R^9 , $C(O)R^9$, $CONR^9R^9$, C_1 - C_4 -alkyl, C_1 - C_4 -alkyl substituted with NR^9R^{10} , C_1 - C_4 -alkyl substituted with OR^{11} , C_2 - C_4 -alkenyl, C_2 - C_4 -alkynyl, C_1 - C_4 -haloalkyl and cyclopropyl;
 R^{8a} is independently selected from halo, nitro, cyano, NR^9R^{10} , OR^{11} , SR^9 , $SO_2NR^9R^9$, SO_2R^9 , CO_2R^9 , $C(O)R^9$, $CONR^9R^9$, C_1 - C_4 -alkyl, C_1 - C_4 -alkyl substituted with NR^9R^{10} , C_1 - C_4 -alkyl substituted with OR^{11} ,
- 30 C_2 - C_4 -alkenyl, C_2 - C_4 -alkynyl, C_1 - C_4 -haloalkyl and C_0 - C_4 -alkylene- R^{8c} ;
 R^{8c} is independently selected from C_3 - C_6 -cycloalkyl and 3- to 7-membered heterocycloalkyl; wherein said heterocycloalkyl group is attached to the C_0 - C_4 -alkylene via a carbon atom in the heterocycloalkyl ring; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R^{13} groups;
- 35 R^9 is independently at each occurrence selected from H and C_1 - C_4 -alkyl; or two R^9 groups, together with the nitrogen atom to which they are attached together form a C_5 - C_8 -heterocycloalkyl group optionally substituted with from 0 to 4 R^{13} groups;
 R^{10} is independently at each occurrence selected from H, C_1 - C_4 -alkyl, $C(O)$ - C_1 - C_4 -alkyl and $S(O)_2$ - C_1 - C_4 -alkyl; or R^9 and R^{10} , together with the nitrogen atom to which they are attached together form a C_5 -
- 40 C_8 -heterocycloalkyl group optionally substituted with from 0 to 4 R^{13} groups;

- R¹¹ is independently at each occurrence selected from H, C₁-C₄-alkyl, C(O)-C₁-C₄-alkyl and C₁-C₄-haloalkyl;
- R¹² is independently selected from C₃-C₆-cycloalkyl, phenyl, 5- or 6- membered heteroaryl and 3- to 6-membered-heterocycloalkyl; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R¹³ groups and wherein said phenyl or heteroaryl group is optionally substituted with from 1 to 3 R¹⁴ groups;
- R¹³ is independently at each occurrence selected from =O, halo, nitro, cyano, NR⁸R⁹, OR¹⁴, SR⁸, SO₂NR⁸R⁸, CO₂R⁸, C(O)R⁸, CONR⁸R⁸, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with OR¹¹, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl, C₆-C₁₀-aryl, and C₃-C₆-cycloalkyl;
- R¹⁴ is independently at each occurrence selected from halo, nitro, cyano, NR⁸R⁹, OR¹⁰, SR⁸, SO₂R⁸, SO₂NR⁸R⁸, CO₂R⁸, C(O)R⁸, CONR⁸R⁸, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl, C₁-C₄-alkyl substituted with OR¹¹, C₁-C₄-alkyl substituted with NR⁸R⁹ and cyclopropyl;
- m is an integer selected from 0, 1, 2, 3 and 4;
- n is an integer selected from 0, 1, 2, 3 and 4;
- p is an integer selected from 0, 1, 2 and 3;
- q is an integer selected from 0, 1 and 2
- wherein any of the aforementioned alkyl, alkylene or cyclopropyl groups is optionally substituted, where chemically possible, by 1 to 5 substituents which are each independently at each occurrence selected from the group consisting of: halo, oxo, fluoro, nitro, cyano, NR^aR^b, OR^a, SR^a, CO₂R^a, C(O)R^a, CONR^aR^a, C₁-C₄-alkyl, C₁-C₄-haloalkyl and cyclopropyl; wherein R^a is independently at each occurrence selected from H, C₁-C₄-alkyl and C₁-C₄-haloalkyl; and R^b is independently at each occurrence selected from H, C₁-C₄-alkyl, C(O)-C₁-C₄-alkyl and S(O)₂-C₁-C₄-alkyl.
2. A compound of clause 1, wherein m is 0 or 1.
 3. A compound of clause 1, wherein m is at least 1, X¹ is carbon and an R¹ group is attached to the X¹ carbon.
 4. A compound of clause 1 or clause 2, wherein n is 0 or 1.
 5. A compound of any one of clauses 1 to 3, wherein p is 0.
 6. A compound of any one of clauses 1 to 4, wherein q is 0.
 7. A compound of any one of clauses 1 to 5, wherein R⁵ is at each occurrence H.
 8. A compound of any one of clauses 1 to 7, wherein X¹, X² and X³ are each carbon.
 9. A compound of any one of clauses 1 to 8, wherein X⁴, X⁵, X⁶ and X⁷ are each carbon.
 10. A compound of any one of clauses 1 to 8, wherein at least one of X⁴, X⁵, X⁶, and X⁷ is nitrogen.
 11. A compound of any one of clauses 1 to 10, wherein X⁸, X⁹ and X¹⁰ are each carbon.
 12. A compound of any one of clauses 1 to 10, wherein a single one of X⁸, X⁹ and X¹⁰ is nitrogen.

13. A compound of any one of clauses 1 to 12, wherein NR^3R^4 has the formula



a is an integer selected from 1 and 2;

R^{4b} is at each occurrence selected from H and F; wherein at least one R^{4b} group is F;

- 5 R^{3a} is independently selected from H and $\text{C}_1\text{-C}_4\text{-alkyl}$;

R^{4c} is independently at each occurrence selected from H, $\text{C}_1\text{-C}_4\text{-alkyl}$ and $\text{C}_4\text{-C}_6\text{-cycloalkyl}$; or

R^{3a} and a single R^{4c} , together with the carbon and nitrogen to which they are attached, form a 4- to 6-membered heterocycloalkyl group.

14. A compound of clause 13, wherein a is 1.

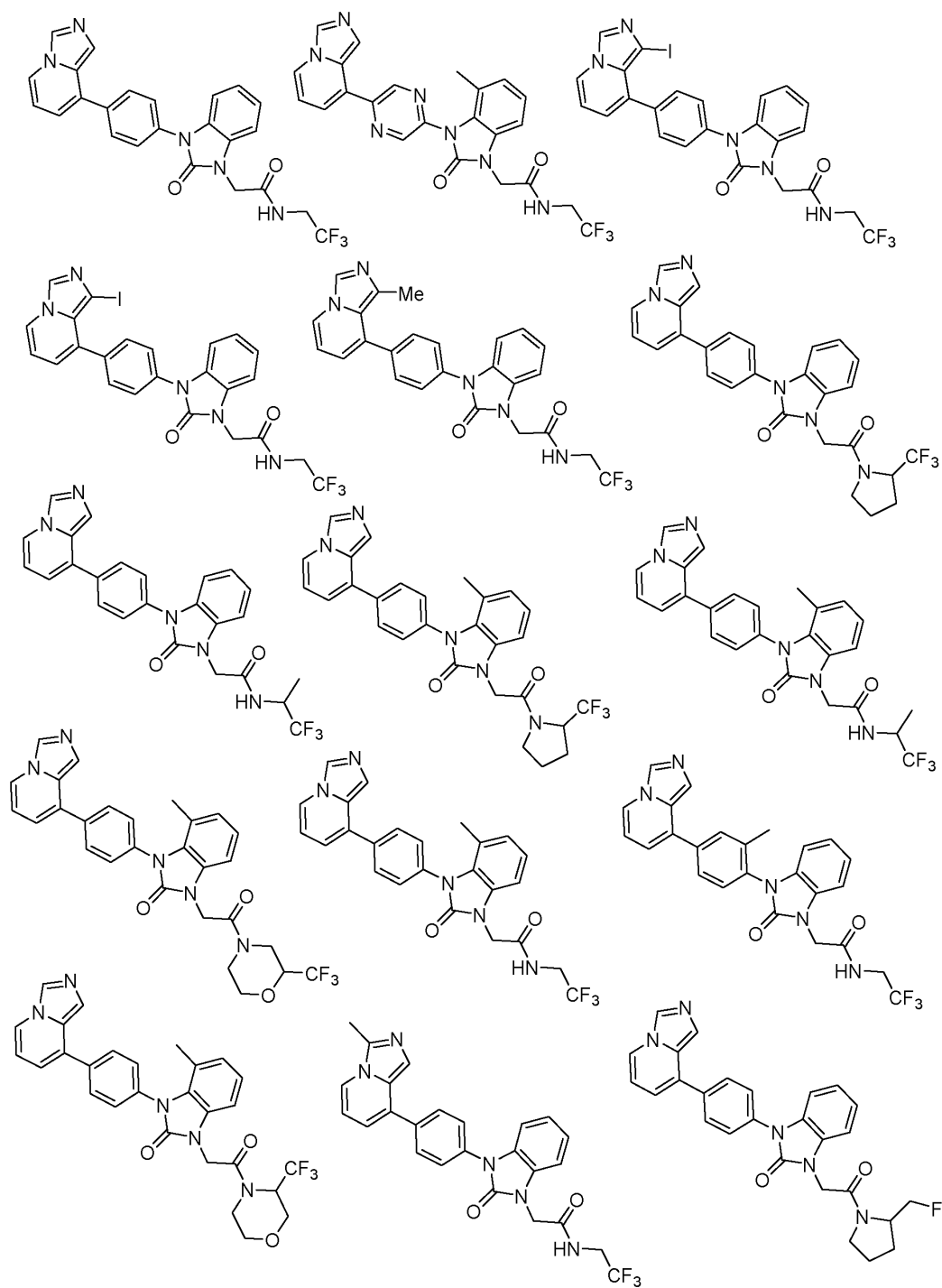
- 10 15. A compound of clause 13 or clause 14, wherein at least two R^{4b} groups are F.

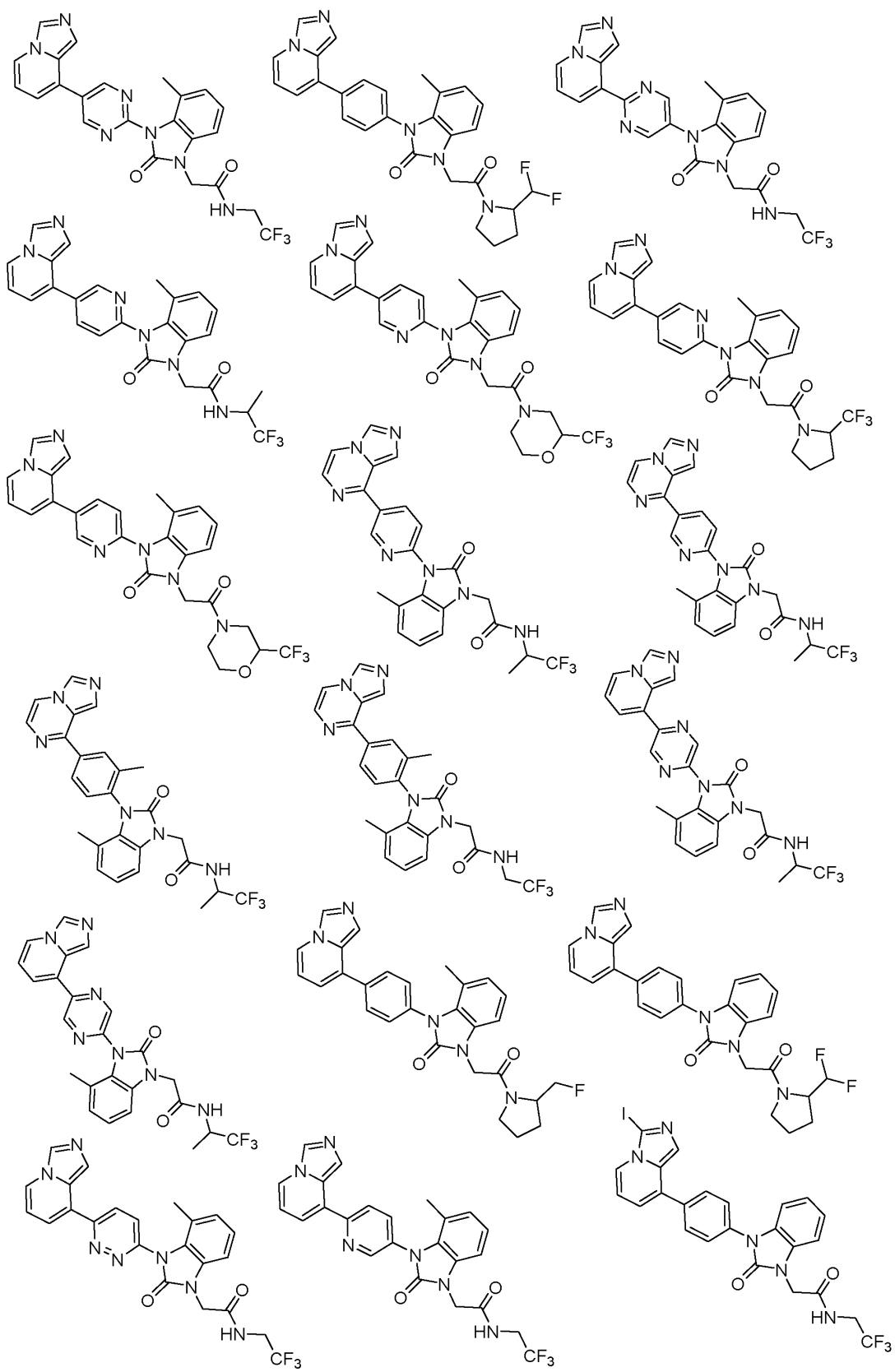
16. A compound of any one of clauses 13 to 15, wherein R^{3a} is H.

17. A compound of any one of clauses 13 to 16, wherein R^{4c} is selected from H and $\text{C}_1\text{-C}_4\text{-alkyl}$.

18. A compound of any one of clauses 13 to 15, wherein R^{3a} and R^{4c} , together with the carbon and nitrogen to which they are attached, form a 4- to 6-membered heterocycloalkyl group.

19. A compound of clause 1, wherein the compound of formula (I) is selected from:





20. A pharmaceutical formulation comprising a compound of any one of clauses 1 to 19 and a pharmaceutically acceptable excipient.

5 21. A compound of any one of clauses 1 to 19 for use as a medicament.

22. A compound of any one of clauses 1 to 19 for use in treating a disease or disorder selected from renal conditions, liver conditions, inflammatory conditions, cardiovascular conditions, acute and chronic organ transplant rejection, fibrotic diseases and cancer.

DETAILED DESCRIPTION

10 [00106] Given below are definitions of terms used in this application. Any term not defined herein takes the normal meaning as the skilled person would understand the term.

[00107] The term “halo” refers to one of the halogens, group 17 of the periodic table. In particular, the term refers to fluorine, chlorine, bromine and iodine. Preferably, the term refers to chlorine or fluorine.

15 [00108] The term “alkyl” refers to a linear or branched hydrocarbon chain. For example, the term “C₁₋₆ alkyl” refers to a linear or branched hydrocarbon chain containing 1, 2, 3, 4, 5 or 6 carbon atoms, for example methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl and *n*-hexyl. “Alkylene” groups may likewise be linear or branched and is divalent, i.e. it attached at two positions to other portions of the molecule. Furthermore, an alkylene group may, for example, correspond to one of those alkyl groups listed in this paragraph. The alkyl and alkylene groups may be unsubstituted or substituted by one or more substituents.

20 [00109] The term “haloalkyl” refers to a hydrocarbon chain substituted with at least one halogen atom independently chosen at each occurrence, for example fluorine, chlorine, bromine and iodine. For example, the term “C₁₋₆ haloalkyl” refers to a linear or branched hydrocarbon chain containing 1, 2, 3, 4, 5 or 6 carbon atoms substituted with at least one halogen. The halogen atom may be present at any position on the hydrocarbon chain. For example, C₁₋₆ haloalkyl may refer to chloromethyl, fluoromethyl, trifluoromethyl, chloroethyl e.g. 1-chloromethyl and 2-chloroethyl, trichloroethyl e.g. 1,2,2-trichloroethyl, 2,2,2-trichloroethyl, fluoroethyl e.g. 1-fluoromethyl and 2-fluoroethyl, trifluoroethyl e.g. 1,2,2-trifluoroethyl and 2,2,2-trifluoroethyl, chloropropyl, trichloropropyl, fluoropropyl, trifluoropropyl. The term “fluoroalkyl” refers to a hydrocarbon chain substituted with at least one fluorine atom..

25 [00110] The term “alkenyl” refers to a branched or linear hydrocarbon chain containing at least one double bond. For example, the term “C₂₋₆ alkenyl” refers to a branched or linear hydrocarbon chain containing at least one double bond and having 2, 3, 4, 5 or 6 carbon atoms. The double bond(s) may be present as the *E* or *Z* isomer. The double bond may be at any possible position of the hydrocarbon chain. For example, the “C₂₋₆ alkenyl” may be ethenyl, propenyl, butenyl, butadienyl, pentenyl, pentadienyl, hexenyl and hexadienyl.

30 [00111] The term “alkynyl” refers to a branched or linear hydrocarbon chain containing at least one triple bond. For example, the term “C₂₋₆ alkynyl” refers to a branched or linear hydrocarbon chain containing at least one triple bond and having 2, 3, 4, 5 or 6 carbon atoms. The triple bond may be at

any possible position of the hydrocarbon chain. For example, the "C₂₋₆ alkynyl" may be ethynyl, propynyl, butynyl, pentynyl and hexynyl.

[00112] The term "heteroalkyl" refers to a branched or linear hydrocarbon chain containing at least one heteroatom selected from N, O and S positioned between any carbon in the chain or at an end of the chain. For example, the term "C₁₋₆ heteroalkyl" refers to a branched or linear hydrocarbon chain containing 1, 2, 3, 4, 5, or 6 carbon atoms and at least one heteroatom selected from N, O and S positioned between any carbon in the chain or at an end of the chain. For example, the hydrocarbon chain may contain one or two heteroatoms. The C₁₋₆ heteroalkyl may be bonded to the rest of the molecule through a carbon or a heteroatom. For example, the "C₁₋₆ heteroalkyl" may be C₁₋₆ *N*-alkyl, C₁₋₆ *N,N*-alkyl, or C₁₋₆ *O*-alkyl.

[00113] The term "heterocycle" refers to a saturated, unsaturated or aromatic ring system containing at least one heteroatom selected from N, O or S. A "heterocyclic" system may contain 1, 2, 3 or 4 heteroatoms, for example 1 or 2. A "heterocyclic" system may be monocyclic or a fused polycyclic ring system, for example, bicyclic or tricyclic. A "heterocyclic" moiety may contain from 3 to 14 carbon atoms, for example, 3 to 8 carbon atoms in a monocyclic system and 7 to 14 carbon atoms in a polycyclic system. "Heterocyclic" encompasses heterocycloalkyl moieties, heterocycloalkenyl moieties and heteroaryl moieties. For example, the heterocyclic group may be: oxirane, aziridine, azetidine, oxetane, tetrahydrofuran, pyrrolidine, imidazolidine, succinimide, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, piperidine, morpholine, thiomorpholine, piperazine, and tetrahydropyran. Heteroaryl includes groups such as pyridones and *N*-alkyl-pyridones.

[00114] The term "C₃₋₈ cycloalkyl" refers to a saturated hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 carbon atoms. For example, the "C₃₋₈ cycloalkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[00115] The term "C₃₋₈ cycloalkenyl" refers to an unsaturated hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 carbon atoms that is not aromatic. The ring may contain more than one double bond provided that the ring system is not aromatic. For example, the "C₃₋₈ cycloalkyl" may be cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadiene, cyclooctenyl and cyclooctadienyl.

[00116] The term "heterocycloalkyl" refers to a saturated hydrocarbon ring system containing carbon atoms and at least one heteroatom within the ring selected from N, O and S. For example, there may be 1, 2 or 3 heteroatoms, optionally 1 or 2. The "heterocycloalkyl" may be bonded to the rest of the molecule through any carbon atom or heteroatom. The "heterocycloalkyl" may have one or more, e.g. one or two, bonds to the rest of the molecule: these bonds may be through any of the atoms in the ring. For example, the "heterocycloalkyl" may be a "C₃₋₈ heterocycloalkyl". The term "C₃₋₈ heterocycloalkyl" refers to a saturated hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 atoms at least one of the atoms being a heteroatom within the ring selected from N, O and S. The "heterocycloalkyl" may be oxirane, aziridine, azetidine, oxetane, tetrahydrofuran, pyrrolidine, imidazolidine, succinimide, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, piperidine, morpholine, thiomorpholine, piperazine, and tetrahydropyran.

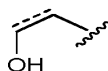
[00117] The term “aromatic” when applied to a substituent as a whole means a single ring or polycyclic ring system with $4n + 2$ electrons in a conjugated π system within the ring or ring system where all atoms contributing to the conjugated π system are in the same plane.

5 [00118] The term “aryl” refers to an aromatic hydrocarbon ring system. The ring system has $4n + 2$ electrons in a conjugated π system within a ring where all atoms contributing to the conjugated π system are in the same plane. For example, the “aryl” may be phenyl and naphthyl. The aryl system itself may be substituted with other groups.

10 [00119] The term “heteroaryl” refers to an aromatic hydrocarbon ring system with at least one heteroatom within a single ring or within a fused ring system, selected from O, N and S. The ring or ring system has $4n + 2$ electrons in a conjugated π system where all atoms contributing to the conjugated π system are in the same plane. For example, the “heteroaryl” may be imidazole, oxazole, isoxazole, thiazole, isothiazole, thiene, furan, thianthrene, pyrrole, benzimidazole, pyrazole, pyrazine, pyridine, pyrimidine and indole.

15 [00120] A bond terminating in a “” represents that the bond is connected to another atom that is not shown in the structure. A bond terminating inside a cyclic structure and not terminating at an atom of the ring structure represents that the bond may be connected to any of the atoms in the ring structure where allowed by valency.

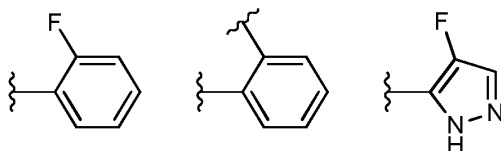
20 [00121] A bond drawn as a solid line and a dotted line represents a bond which can be either a single bond or a double bond, where chemically possible. For example, the bond drawn below could be a single bond or a double bond.



25 [00122] Where a moiety is substituted, it may be substituted at any point on the moiety where chemically possible and consistent with atomic valency requirements. The moiety may be substituted by one or more substituents, e.g. 1, 2, 3 or 4 substituents; optionally there are 1 or 2 substituents on a group. Where there are two or more substituents, the substituents may be the same or different.

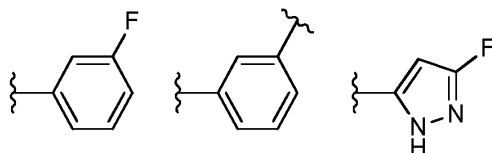
[00123] Substituents are only present at positions where they are chemically possible, the person skilled in the art being able to decide (either experimentally or theoretically) without inappropriate effort which substitutions are chemically possible and which are not.

30 [00124] Ortho, meta and para substitution are well understood terms in the art. For the absence of doubt, “ortho” substitution is a substitution pattern where adjacent carbons possess a substituent, whether a simple group, for example the fluoro group in the example below, or other portions of the molecule, as indicated by the bond ending in “”.



35 [00125] “Meta” substitution is a substitution pattern where two substituents are on carbons one carbon removed from each other, i.e with a single carbon atom between the substituted carbons. In other words

there is a substituent on the second atom away from the atom with another substituent. For example the groups below are meta substituted.



5 [00126] "Para" substitution is a substitution pattern where two substituents are on carbons two carbons removed from each other, i.e. with two carbon atoms between the substituted carbons. In other words there is a substituent on the third atom away from the atom with another substituent. For example the groups below are para substituted.



10 [00127] Throughout the description the disclosure of a compound also encompasses pharmaceutically acceptable salts, solvates and stereoisomers thereof.

[00128] Where a compound has a stereocentre, both (*R*) and (*S*) stereoisomers are contemplated by the invention, equally mixtures of stereoisomers or a racemic mixture are contemplated by the present application. Where a compound of the invention has two or more stereocentres any combination of (*R*) and (*S*) stereoisomers is contemplated. The combination of (*R*) and (*S*) stereoisomers may result in a diastereomeric mixture or a single diastereoisomer. The compounds of the invention may be present as a single stereoisomer or may be mixtures of stereoisomers, for example racemic mixtures and other enantiomeric mixtures, and diastereomeric mixtures. Where the mixture is a mixture of enantiomers the enantiomeric excess may be any of those disclosed above. Where the compound is a single stereoisomer the compounds may still contain other diastereoisomers or enantiomers as impurities.

20 Hence a single stereoisomer does not necessarily have an enantiomeric excess (e.e.) or diastereomeric excess (d.e.) of 100% but could have an e.e. or d.e. of about at least 85%, at least 60% or less. For example, the e.e. or d.e. may be 90% or more, 90% or more, 80% or more, 70% or more, 60% or more, 50% or more, 40% or more, 30% or more, 20% or more, or 10% or more.

[00129] The invention contemplates pharmaceutically acceptable salts of the compounds of the invention. These may include the acid addition and base salts of the compounds. These may be acid addition and base salts of the compounds. In addition the invention contemplates solvates of the compounds. These may be hydrates or other solvated forms of the compound.

[00130] Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulfate/sulfate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthylate, 1,5-naphthalenedisulfonate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

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[00131] Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts. Hemisalts of acids and bases may also be formed, for example, hemisulfate and hemicalcium salts. For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

[00132] Pharmaceutically acceptable salts of compounds of formula (I) may be prepared by one or more of three methods:

- (i) by reacting the compound of the invention with the desired acid or base;
- (ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of the invention or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or
- (iii) by converting one salt of the compound of the invention to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

[00133] All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

[00134] The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

[00135] Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non-ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Halebian (August 1975).

[00136] Hereinafter all references to compounds of any formula include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

[00137] The compounds of the invention include compounds of a number of formula as herein defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labelled compounds of the invention.

[00138] The present invention also includes all pharmaceutically acceptable isotopically-labelled compounds of the invention wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature.

[00139] Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^2H and ^3H , carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such

as ^{18}F , iodine, such as ^{123}I and ^{125}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , and sulphur, such as ^{35}S .

[00140] Certain isotopically-labelled compounds, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^3H , and carbon-14, i.e. ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

[00141] Substitution with heavier isotopes such as deuterium, i.e. ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

10 [00142] Before purification, the compounds of the present invention may exist as a mixture of enantiomers depending on the synthetic procedure used. The enantiomers can be separated by conventional techniques known in the art. Thus the invention covers individual enantiomers as well as mixtures thereof.

15 [00143] For some of the steps of the process of preparation of the compounds of the invention, it may be necessary to protect potential reactive functions that are not wished to react, and to cleave said protecting groups in consequence. In such a case, any compatible protecting radical can be used. In particular methods of protection and deprotection such as those described by T.W. GREENE (Protective Groups in Organic Synthesis, A. Wiley- Interscience Publication, 1981) or by P. J. Kocienski (Protecting groups, Georg Thieme Verlag, 1994), can be used. All of the above reactions and the preparations of novel starting materials used in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well-known to those skilled in the art with reference to literature precedents and the examples and preparations hereto.

20 [00144] Also, the compounds of the present invention as well as intermediates for the preparation thereof can be purified according to various well-known methods, such as for example crystallization or chromatography.

25 [00145] One or more compounds of the invention may be combined with one or more pharmaceutical agents, for example anti-inflammatory agents, anti-fibrotic agents, chemotherapeutics, anti cancer agents, immunosuppressants, anti-tumour vaccines, cytokine therapy, or tyrosine kinase inhibitors, for the treatment of conditions modulated by the inhibition of ROCK, for example fibrotic diseases, auto-immune, inflammatory-fibrotic conditions, inflammatory conditions, central nervous system disorders, or cancer.

30 [00146] The method of treatment or the compound for use in the treatment of renal conditions, liver conditions, inflammatory conditions, cardiovascular conditions, acute and chronic organ transplant rejection, fibrotic diseases and cancer as defined hereinbefore may be applied as a sole therapy or be a combination therapy with an additional active agent.

[00147] The method of treatment or the compound for use in the treatment of renal conditions, liver conditions, inflammatory conditions, cardiovascular conditions, acute and chronic organ transplant rejection, fibrotic diseases and cancer. The additional active agents may be one or more active agents

used to treat the condition being treated by the compound of the invention and additional active agent. The additional active agents may include one or more of the following active agents:-

- (i) steroids such as corticosteroids, including glucocorticoids and mineralocorticoids, for example aclometasone, aclometasone dipropionate, aldosterone, amcinonide, beclomethasone, beclomethasone dipropionate, betamethasone, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone valerate, budesonide, clobetasone, clobetasone butyrate, clobetasol propionate, cloprednol, cortisone, cortisone acetate, cortivazol, deoxycortone, desonide, desoximetasone, dexamethasone, dexamethasone sodium phosphate, dexamethasone isonicotinate, difluorocortolone, flucorolone, flumethasone, flunisolide, fluocinolone, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluocortolone caproate, fluocortolone pivalate, fluorometholone, fluprednidene, fluprednidene acetate, flurandrenolone, fluticasone, fluticasone propionate, halcinonide, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone aceponate, hydrocortisone buteprate, hydrocortisone valerate, icomethasone, icomethasone enbutate, meprednisone, methylprednisolone, mometasone paramethasone, mometasone furoate monohydrate, prednicarbate, prednisolone, prednisone, tixocortol, tixocortol pivalate, triamcinolone, triamcinolone acetonide, triamcinolone alcohol and their respective pharmaceutically acceptable derivatives. A combination of steroids may be used, for example a combination of two or more steroids mentioned in this paragraph;

- (ii) TNF inhibitors for example etanercept; monoclonal antibodies (e.g. infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi)); fusion proteins (e.g. etanercept (Enbrel)); and 5-HT_{2A} agonists (e.g. 2,5-dimethoxy-4-iodoamphetamine, TCB-2, lysergic acid diethylamide (LSD), lysergic acid dimethylazetidine);

(iii) anti-inflammatory drugs, for example non-steroidal anti-inflammatory drugs;

- (iv) dihydrofolate reductase inhibitors/antifolates, for example methotrexate, trimethoprim, brodimoprim, tetroxoprim, iclaprim, pemetrexed, ralitrexed and pralatrexate; and

- (v) immunosuppressants for example cyclosporins, tacrolimus, sirolimus pimecrolimus, angiotensin II inhibitors (e.g. Valsartan, Telmisartan, Losartan, Irbesatan, Azilsartan, Olmesartan, Candesartan, Eprosartan) and ACE inhibitors e.g. sulfhydryl-containing agents (e.g. Captopril, Zofenopril), dicarboxylate-containing agents (e.g. Enalapril, Ramipril, Quinapril, Perindopril, Lisinopril, Benazepril, Imidapril, Zofenopril, Trandolapril), phosphate-containing agents (e.g. Fosinopril), casokinins, lactokinins and lactotripeptides.

- (vi) Anti-fibrotic agents for example: Pirfenidone, Nintedanib, Anti-IL-13 monoclonal antibodies (e.g. Tralokinumab, QAX576, Lebrikizumab), simtuzumab, FG-3019, lysophosphatidic acid receptor antagonists (e.g. BMS-986020, AM966), LOXL2 inhibitors, BET bromodomain inhibitors (e.g. JQ1), HDAC inhibitors (e.g. Vorinostat), thrombin inhibitors (e.g. Dabigatran), FactorXa inhibitors (e.g. Apixban, Rivaroxaban) 15PGDH inhibitors, anti- $\alpha\text{v}\beta\text{6}$ monoclonal antibodies (e.g. BG00011), Anti-CTGF monoclonal antibodies (e.g. FG-3019), PAR1 inhibitors, Nox4 inhibitors and PAI-1 inhibitors.

- [00148]** The method of treatment or the compound for use in the treatment of cancer may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumor agents:

- (i) antiproliferative/antineoplastic drugs and combinations thereof, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, uracil mustard, bendamustine, melphalan, chlorambucil, chlormethine, busulphan, temozolamide, nitrosoureas, ifosamide, melphalan, pipobroman, triethylene-melamine, triethylenethiophosphoramine, carmustine, lomustine, streptozocin and dacarbazine); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, pemetrexed, cytosine arabinoside, floxuridine, cytarabine, 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, pentostatin, and gemcitabine and hydroxyurea); antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinese inhibitors); proteasome inhibitors, for example carfilzomib and bortezomib; interferon therapy; and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, mitoxantrone and camptothecin); bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, ara-C, paclitaxel (Taxol™), nabpaclitaxel, docetaxel, mithramycin, deoxyco-formycin, mitomycin-C, L-asparaginase, interferons (especially IFN- α), etoposide, and teniposide;
- (ii) cytostatic agents such as antiestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and idoxifene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase such as finasteride; and navelbine, CPT-II, anastrozole, letrozole, capecitabine, reloxafine, cyclophosphamide, ifosamide, and droloxafine;
- (iii) anti-invasion agents, for example dasatinib and bosutinib (SKI-606), and metalloproteinase inhibitors, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase;
- (iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies, for example the anti-erbB2 antibody trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti-erbB1 antibody cetuximab, tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as gefitinib, erlotinib, 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib) and antibodies to costimulatory molecules such as CTLA-4, 4-1BB and PD-1, or antibodies to cytokines (IL-10, TGF- β); inhibitors of the hepatocyte growth factor family; inhibitors of the insulin growth factor family; modulators of protein regulators of cell apoptosis (for example Bcl-2 inhibitors); inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib, tipifarnib and lonafarnib), inhibitors of cell signalling through MEK and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, PI3 kinase inhibitors, Plt3 kinase inhibitors,

CSF-1R kinase inhibitors, IGF receptor, kinase inhibitors; aurora kinase inhibitors and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors; and CCR2, CCR4 or CCR6 modulator;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™); thalidomide; lenalidomide; and for example, a VEGF receptor tyrosine kinase inhibitor such as vandetanib, vatalanib, sunitinib, axitinib and pazopanib;

(vi) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2;

(vii) immunotherapy approaches, including for example antibody therapy such as alemtuzumab, rituximab, ibritumomab tiuxetan (Zevalin®) and ofatumumab; interferons such as interferon α ; interleukins such as IL-2 (aldesleukin); interleukin inhibitors for example IRAK4 inhibitors; cancer vaccines including prophylactic and treatment vaccines such as HPV vaccines, for example Gardasil, Cervarix, Oncophage and Sipuleucel-T (Provenge); gp100; dendritic cell-based vaccines (such as Ad.p53 DC); and toll-like receptor modulators for example TLR-7 or TLR-9 agonists; and

(viii) cytotoxic agents for example fludarabine (fludara), cladribine, pentostatin (Nipent™);

(ix) steroids such as corticosteroids, including glucocorticoids and mineralocorticoids, for example aclometasone, aclometasone dipropionate, aldosterone, amcinonide, beclomethasone, beclomethasone dipropionate, betamethasone, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone valerate, budesonide, clobetasone, clobetasone butyrate, clobetasol propionate, cloprednol, cortisone, cortisone acetate, cortivazol, deoxycortone, desonide, desoximetasone, dexamethasone, dexamethasone sodium phosphate, dexamethasone isonicotinate, difluorocortolone, flucorolone, flumethasone, flunisolide, fluocinolone, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluocortolone caproate, fluocortolone pivalate, fluorometholone, fluprednidene, fluprednidene acetate, flurandrenolone, fluticasone, fluticasone propionate, halcinonide, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone aceponate, hydrocortisone buteprate, hydrocortisone valerate, icomethasone, icomethasone enbutate, meprednisone, methylprednisolone, mometasone paramethasone, mometasone furoate monohydrate, prednicarbate, prednisolone, prednisone, tixocortol, tixocortol pivalate, triamcinolone, triamcinolone acetonide, triamcinolone alcohol and their respective pharmaceutically acceptable derivatives. A combination of steroids may be used, for example a combination of two or more steroids mentioned in this paragraph;

(x) targeted therapies, for example PI3Kd inhibitors, for example idelalisib and perifosine; PD-1, PD-L1, PD-L2 and CTL4-A modulators, antibodies and vaccines; other IDO inhibitors (such as indoximod); anti-PD-1 monoclonal antibodies (such as MK-3475 and nivolumab); anti-PD-L1 monoclonal antibodies (such as MEDI-4736 and RG-7446); anti-PD-L2 monoclonal antibodies; and anti-CTLA-4 antibodies (such as ipilimumab);

(xii) chimeric antigen receptors, anticancer vaccines and arginase inhibitors.

[00149] Such combination treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the

compounds of this invention within a therapeutically effective dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

5 [00150] Compounds of the invention may exist in a single crystal form or in a mixture of crystal forms or they may be amorphous. Thus, compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, or spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

10 [00151] For the above-mentioned compounds of the invention the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. For example, if the compound of the invention is administered orally, then the daily dosage of the compound of the invention may be in the range from 0.01 micrograms per kilogram body weight ($\mu\text{g/kg}$) to 100 milligrams per kilogram body weight (mg/kg).

15 [00152] A compound of the invention, or pharmaceutically acceptable salt thereof, may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the compounds of the invention, or pharmaceutically acceptable salt thereof, is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

20 [00153] Depending on the mode of administration of the compounds of the invention, the pharmaceutical composition which is used to administer the compounds of the invention will preferably comprise from 0.05 to 99 %w (per cent by weight) compounds of the invention, more preferably from 0.05 to 80 %w compounds of the invention, still more preferably from 0.10 to 70 %w compounds of the invention, and even more preferably from 0.10 to 50 %w compounds of the invention, all percentages by weight being based on total composition.

25 [00154] The pharmaceutical compositions may be administered topically (e.g. to the skin) in the form, e.g., of creams, gels, lotions, solutions, suspensions, or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of a sterile solution, suspension or emulsion for injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion); by rectal administration in the form of suppositories; or by inhalation in the form of an aerosol.

30 [00155] For oral administration the compounds of the invention may be admixed with an adjuvant or a carrier, for example, lactose, saccharose, sorbitol, mannitol; a starch, for example, potato starch, corn starch or amylopectin; a cellulose derivative; a binder, for example, gelatine or polyvinylpyrrolidone; and/or a lubricant, for example, magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatine, talcum and titanium dioxide. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

35 [00156] For the preparation of soft gelatine capsules, the compounds of the invention may be admixed with, for example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules

of the compound using either the above-mentioned excipients for tablets. Also liquid or semisolid formulations of the compound of the invention may be filled into hard gelatine capsules. Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing the compound of the invention, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, sweetening agents (such as saccharine), preservative agents and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

[00157] For intravenous (parenteral) administration the compounds of the invention may be administered as a sterile aqueous or oily solution.

[00158] The size of the dose for therapeutic purposes of compounds of the invention will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

[00159] Dosage levels, dose frequency, and treatment durations of compounds of the invention are expected to differ depending on the formulation and clinical indication, age, and co-morbid medical conditions of the patient.

[00160] Throughout the description and claims of this specification, the words "comprise" and "contain" and variations of them mean "including but not limited to", and they are not intended to (and do not) exclude other moieties, additives, components, integers or steps. Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

[00161] Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. The invention is not restricted to the details of any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

[00162] The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

[00163] The compounds of the invention may be prepared according to or analogously to the General Schemes 1 – 5 and Examples 1 to 57.

EXAMPLES AND SYNTHESIS

Experimental Procedures

Solvents, reagents and starting materials were purchased from commercial vendors and used as received unless otherwise described. All reactions were performed at room temperature unless otherwise stated. Compound identity and purity confirmations were performed by LCMS UV using a Waters Acquity SQ Detector 2 (ACQ-SQD2#LCA081). The diode array detector wavelength was set to

5 acquire spectra at a wavelength of 254 nm and the MS was in positive and negative electrospray mode (m/z : 150-800). A 2 μ L aliquot was injected onto a guard column (0.2 μ m x 2 mm filters) and UPLC column (C18, 50 x 2.1 mm, < 2 μ m) in sequence maintained at 40 °C. The samples were eluted at a flow rate of 0.6 mL/min with a mobile phase system composed of A (0.1% (v/v) Formic Acid in Water) and B (0.1% (v/v) Formic Acid in Acetonitrile) according to the gradients outlined in Table 1 below

10 (Methods 1 and 2). Retention times RT are reported in minutes. The following methods were also used on occasions when described throughout the experimental section, gradients are detailed in table 1. Method 3 utilised a Shimadzu 2020 series spectrometer equipped with a binary pump and diode array detector (acquisition wavelength 214 and 254 nm) and the MS was in positive and negative electrospray mode (m/z : 100-900). 2 μ L Aliquot were injected onto an Agilent Poroshell 120 EC-C18 column (2.7

15 μ m, 4.6x50 mm) maintained at 35°C and eluted at 1.0ml/min using mobile phase consisting of : A: 0.05% Formic acid in water (v/v), B: 0.05% Formic acid in ACN(v/v). Method 4 utilised an Agilent Technologies 1290 series spectrometer equipped with a binary pump and diode array detector (acquisition wavelength 214 and 254 nm) and the MS was in positive electrospray mode (m/z : 70-1000). 2 μ L Aliquots were injected onto an Agilent Eclipse Plus RRHD C18, (1.8 μ m, 3.0x50 mm) column maintained at 40 °C and

20 eluted at 0.8 mL/min using mobile phase consisting of : A: 0.05% Formic acid in water (v/v), B: 0.05% Formic acid in ACN(v/v).

Method 1 (Long acidic)		
Time (min)	%A	%B
0	95	5
1.1	95	5
6.1	5	95
7	5	95
7.5	95	5
8	95	5
Method 2 (Short acidic)		
Time (min)	A	%B
0	95	5
0.3	95	5
2	5	95
2.6	95	5
3	95	5
Method 3		
Time (min)	%A	%B
0.01	85	15

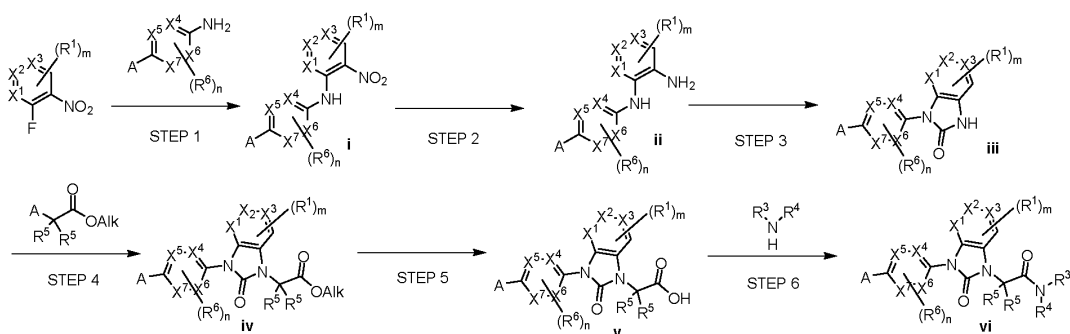
5 Compound purification was performed by flash column chromatography on silica or by preparative LCMS. LCMS purification was performed using a Waters 3100 Mass detector in positive and negative electrospray mode (m/z : 150-800) with a Waters 2489 UV/Vis detector. Samples were eluted at a flow rate of 20 mL/min on a XBridge™ prep C18 5 μ M OBD 19x100 mm column with a mobile phase system composed of A (0.1% (v/v) Formic Acid in Water) and B (0.1% (v/v) Formic Acid in Acetonitrile) according to the gradient outlined in Table 2 below.

Time (min)	%A	%B
0	90	10
1.5	90	10
11.7	5	95
13.7	5	95
14	90	90
15	90	90

Table 2.

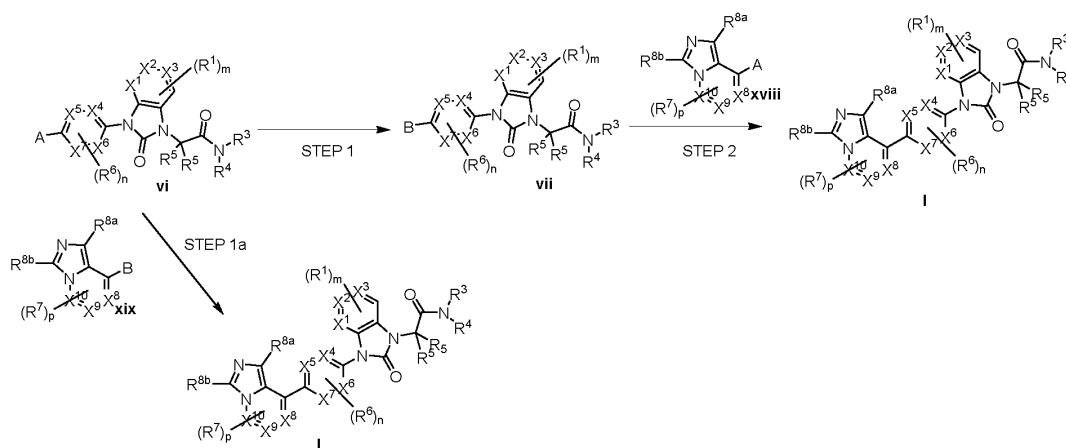
General routes and Schemes

General Scheme 1



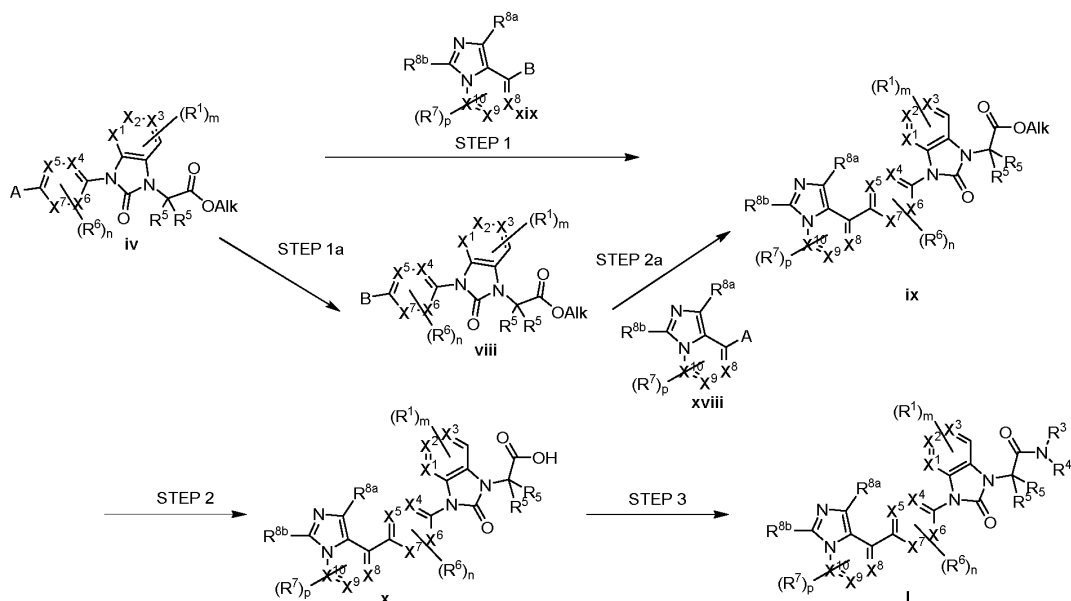
Compounds of formula (I) can be prepared from intermediates represented by **vi** in general scheme 1. In Step 1 an *ortho*-fluoronitroaryl compound undergoes a nucleophilic displacement reaction with an aryl or heteroarylamine (where A represents a halogen such as Cl, Br or I capable of participating in a metal mediated cross-coupling reaction such as a Suzuki or Stille reaction), in the presence of a base such as sodium hydride, to afford compounds of structure **i**. In step 2 the nitro group of **i** can be reduced by transition metal catalysis in the presence of hydrogen gas or using an alternative source of hydrogen such as ammonium chloride to produce compounds of structure **ii**. In step 3 reaction with a carbonyl equivalent (for example CDI) affords cyclized products represented by **iii**. In step 4 the free NH of **iii** is reacted with an appropriate α -halo ester, where A is a halogen such as Br and OAlk represents an alkoxy group such as ethoxide which is subsequently hydrolysed to the corresponding carboxylic acid in step 5 under basic conditions with KOH or LiOH, affording compounds of structure **v**. Reaction with an appropriate amine in step 6 using a carboxylic acid activating reagent such as HATU and a base such as DIPEA affords intermediates represented by **vi**.

General Scheme 2



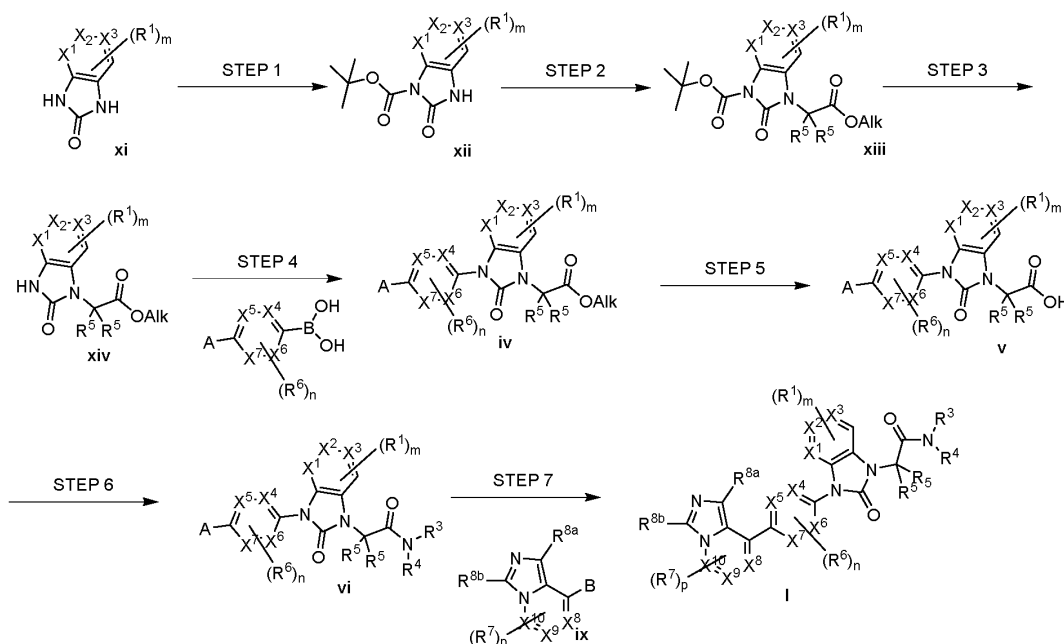
Compounds of formula **I** can be synthesised from intermediates represented by general structure **vi** via the two routes described in general scheme 2. According to step 1a, **vi** (in which A represents a halogen such as Br or another leaving group capable of participating in a metal catalysed cross-coupling reaction such as a triflate) undergoes transition metal catalysed cross-coupling with an azimidazole of structure **xix** in which B is a boronic acid, boronate ester or stannyl group (trialkyl tin) capable of participating in a Suzuki or Stille type reaction with a compound of structure **vi**. As an example A may be a boronic acid pinacol ester and B may be a bromide and these groups in step 1a undergo a Suzuki reaction catalysed by Pd(dppf)Cl₂·DCM in the presence of K₂CO₃ KOAc to afford a compound of formula **I**. Alternatively, according to step 1 the intermediate of structure **vi** can be converted into a boronate or stannane of formula **vii** via reaction with bis(pinacolato)diboron or tributyltin chloride respectively (where B is a boronic acid, boronate ester or stannyl group (trialkyl tin) and undergo subsequent Suzuki or Stille reaction in Step 2 with an azimidazole of structure **xviii** where A is a halogen such as Br, Cl or I, affording compounds of formula (**I**).

General Scheme 3



- Compounds of formula (I) may also be accessed by re-ordering the steps from general schemes 1 and 2 as depicted in general scheme 3. The definitions of groups A, B and OAlk in structures shown in general scheme 3 are the same as those described for general schemes 1 and 2. In step 1 intermediates of structure (iv) undergo metal catalysed cross-coupling reactions such as Suzuki or Stille reactions with boronate or stannane derivatives of azaimidazoles represented by (xix). In step 2 the cross-coupled products ((ix)) undergo base mediated ester hydrolysis as previously described and then amide coupling in step 3 to afford compounds of formula (I). Alternatively the cross-coupling partners can be reversed by converting halide or triflate (iv), to the corresponding boronate or stannane in step 1a and reacting this with a haloazaimidazole of structure (xviii) in step 2b to afford intermediates of structure (ix).

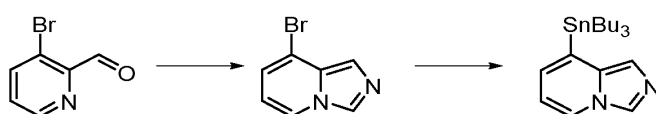
General Scheme 4



General scheme 4 outlines an alternative route to prepare intermediates of structure **iv** which are then transformed into intermediate **vi** (general Scheme 1) which can then be converted into compounds of formula (**I**) via the methods described in general scheme 2. In step 1 an appropriate benzimidazolone or azabenzimidazolone derivative (**xi**) is mono-Boc protected using NaH and di-tert-butyl dicarbonate. In step 2 the remaining free NH of **xii** is alkylated with an appropriate α -haloester. In step 3 the boc protecting group of **xiii** is removed using TFA to allow for Chan-Lam type coupling of **xiv** and an appropriate aryl boronic acid using copper (II) acetate as a catalyst and air as a source of oxygen in step 4 to afford intermediates of structure **iv**.

10 General Scheme 5

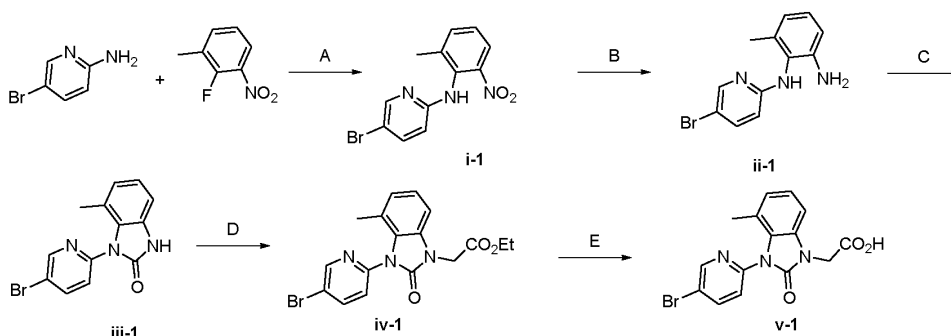
Synthesis of Intermediates



Ammonium acetate (20.7 g, 268.8 mmol) was added to a stirred solution of formaldehyde (36.5-38% in water) (17 mL, 215.04 mmol) and acetic acid (50 mL) at room temperature. The mixture was allowed to stir for 10 minutes and then 3-bromopicolinaldehyde (5.0 g, 26.88 mmol) was added portion-wise over 1 hour. The reaction was allowed to stir for a further hour and then solvent removed in vacuo. The residue was partitioned between sat. aq. NaHCO_3 (200 mL) and DCM (200 mL). The organic layer was separated and the aqueous extracted with DCM (200 mL). The combined organic layers were dried over sodium sulfate and solvent removed in vacuo. The residue was purified by column chromatography eluting with 0-5% MeOH in DCM to give 8-bromoimidazo[1,5-a]pyridine (1.7 g, 8.63 mmol, 32% yield) as a brown solid. UPLC-MS (ES⁺, Method 1): 0.78 min, m/z 196.8, 198.8 $[\text{M}]^+ / [\text{M}+2]^+$

To a solution of 8-bromo-imidazo[1,5-a]pyridine (1.00 g, 5.08 mmol) in m-xylene (15 mL) was added bis(tributyltin) (3.08 mL, 6.09 mmol) with Pd(PPh₃)₄ (0.59 g, 0.51 mmol) at 25 °C. The resulting mixture was heated at 130 °C under a nitrogen atmosphere overnight. The crude reaction was purified by flash column chromatography eluting with Pet.Ether/EtOAc (1:1) affording tributyl(imidazo[1,5-a]pyridin-8-yl)stannane (1.04 g, 2.55 mmol, 50% yield). UPLC-MS (ES⁺, Method 4): 2.24 min, m/z 409.0 [M+H]⁺

Route 1



Step A: Synthesis of **i-1**: Sodium hydride, (1.73 g, 43.35 mmol, 60% dispersion in mineral oil) was added in 100 mg portions to a stirred solution of 2-amino-5-bromopyridine (5.00 g, 28.90 mmol) in THF (300 mL). 20 minutes after addition was complete 2-fluoro-3-nitrotoluene (4.93 g, 31.79 mmol) was added, the reaction mixture was heated to 50 °C and left to stir for 6 hours. The reaction mixture was left to cool to room temperature before water and EtOAc were added and the layers separated. The aqueous layer was extracted with further EtOAc. Organic fractions were collected, passed through phase separating filter paper and the solvent reduced in vacuo to afford the crude product as a dark red brown oil. The crude material was purified by flash column chromatography eluting with 0 - 100% EtOAc in Pet. ether to afford the desired product 5-bromo-N-(2-methyl-6-nitro-phenyl)pyridin-2-amine (3.44 g, 11.16 mmol, 39% yield) as a brown solid.

UPLC-MS (ES⁺, Method 2): 1.82 min, m/z 309.9 [M+2]⁺

¹H NMR (400 MHz, DMSO-d₆) δ 8.87 (s, 1H), 7.99 - 7.94 (m, 1H), 7.77 - 7.69 (m, 2H), 7.63 - 7.58 (m, 1H), 7.33 - 7.26 (m, 1H), 6.77 (dd, J = 8.9, 0.5 Hz, 1H), 2.27 (s, 3H) ppm.

Step B: Synthesis of **ii-1**: Iron (3.12 g, 55.82 mmol) was added to a stirring mixture of 5-bromo-N-(2-methyl-6-nitro-phenyl)pyridin-2-amine (3.44 g, 11.16 mmol) and ammonium chloride (2.99 g, 55.82 mmol) in ethanol (45 mL) and water (9 mL) at rt. The reaction was heated to 75 °C and left to stir for 30 minutes. The mixture was allowed to cool to room temperature and the solvents removed in vacuo. The black residue was taken up in DCM and filtered under vacuum, washing with DCM and the solvents removed in vacuo. The desired product N2-(5-bromo-2-pyridyl)-3-methyl-benzene-1,2-diamine (3.10 g, 11.15 mmol, 99.8% yield) as afforded as a dark purple solid which was used in the next step directly. Reaction assumed quantitative.

UPLC-MS (ES⁺, Method 2): 1.59 min, m/z 277.9 / 279.9 [M]⁺ / [M+2]⁺

¹H NMR (400 MHz, DMSO-d₆) δ 8.04 (br s, 1H), 7.91 (br s, 1H), 7.57 (br s, 1H), 6.88 (br s, 1H), 6.60 (br s, 1H), 6.46 (br s, 1H), 6.18 (br s, 1H), 4.76 (br s, 2H), 2.02 (s, 3H) ppm.

Step C: Synthesis of **iii-1**: 1,1'-Carbonyldiimidazole (4.66 g, 28.76 mmol) was added to a stirring solution of N2-(5-bromo-2-pyridyl)-3-methyl-benzene-1,2-diamine (3.20 g, 11.50 mmol) in DMF (45 mL) at room temperature. The reaction was heated to 70 °C and stirred for 30 minutes. The reaction was cooled to room temperature and solvent removed in vacuo to afford a dark purple residue. Water was added, a solid precipitated. The solids were collected via filtration, washing with copious amounts of water and left to dry overnight to afford the desired product 3-(5-bromo-2-pyridyl)-4-methyl-1H-benzimidazol-2-one (2.80 g, 9.21 mmol, 80.0% yield).

UPLC-MS (ES⁺, Method 2): 1.83 min, m/z 303.9 / 305.9 [M]⁺ / [M+2]⁺

Step D: Synthesis of **iv-1**: Ethyl bromoacetate (1.91 mL, 17.26 mmol) was added to a stirring solution of 3-(5-bromo-2-pyridyl)-4-methyl-1H-benzimidazol-2-one (3.50 g, 11.51 mmol) and cesium carbonate (7.50 g, 23.01 mmol) in MeCN (50 mL). The reaction mixture was heated to 50 °C and left to stir for 24 hours. LCMS showed product formation. The reaction mixture was left to cool to room temperature before water and EtOAc were added and the layers separated. The aqueous layer was extracted with further EtOAc. Organic fractions were collected, passed through phase separating filter paper and the solvent reduced in vacuo to afford the crude product as a dark brown oil. The crude material was purified by flash column chromatography (eluting in 0 - 100% EtOAc in Pet. ether) to afford the desired product ethyl 2-[3-(5-bromo-2-pyridyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetate (3.59 g, 9.20 mmol, 80% yield) as a light brown solid. **UPLC-MS** (ES⁺, Method 2): 1.94 min, m/z 390.0 / 392.0 [M]⁺ / [M+2]⁺

¹H NMR (400 MHz, DMSO-d₆) δ 8.79 (dd, J = 8.5, 0.5 Hz, 1H), 8.31 (dd, J = 8.4, 2.6 Hz, 1H), 7.64 (dd, J = 8.5, 0.5 Hz, 1H), 7.14 - 7.10 (m, 1H), 7.09 - 7.04 (m, 1H), 6.92 - 6.87 (m, 1H), 4.78 (s, 2H), 4.17 (q, J = 7.1 Hz, 2H), 1.85 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H) ppm.

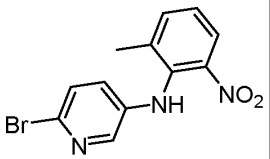
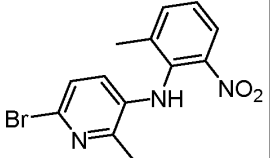
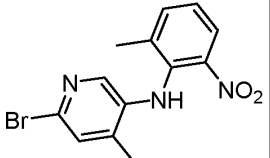
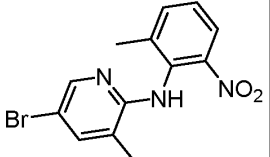
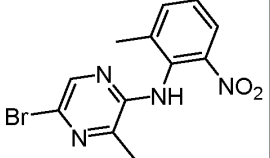
Step E: Synthesis of **v-1**: Ethyl 2-[3-(5-bromo-2-pyridyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetate (3.59 g, 9.20 mmol) was stirred in sodium hydroxide (50 mL, 50 mmol) (1M) and THF (50 mL) at room temperature for 30 minutes. The reaction mixture was then acidified to ~pH5 using conc. HCl. EtOAc was added and the layers separated. The aqueous layer was extracted with further EtOAc. Organic fractions were collected, passed through phase separating filter paper and the solvent reduced in vacuo to afford the crude product 2-[3-(5-bromo-2-pyridyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetic acid (3.33 g, 9.19 mmol, 100% yield) as a grey solid. Material taken onto the next stage without any further purification. **UPLC-MS** (ES⁺, Method 2): 1.52 min, m/z 362.0 / 363. [M]⁺ / [M+2]⁺

¹H NMR (400 MHz, DMSO-d₆) δ 13.21 (br s, 1H), 8.78 (dd, J = 8.6, 0.6 Hz, 1H), 8.31 (dd, J = 8.4, 2.6 Hz, 1H), 7.64 (dd, J = 8.4, 0.6 Hz, 1H), 7.13 - 7.09 (m, 1H), 7.09 - 7.03 (m, 1H), 6.90 - 6.86 (m, 1H), 4.65 (s, 2H), 1.85 (s, 3H) ppm.

Intermediates synthesised following the same procedure as intermediate **i-1** (Route 1) replacing 2-amino-5-bromopyridine and 2-fluoro-3-nitrotoluene in Step A for the described building blocks are described in Table 3.

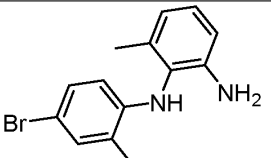
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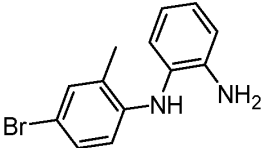
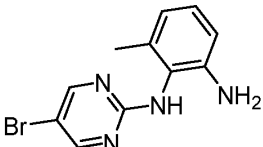
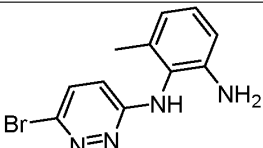
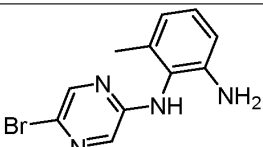
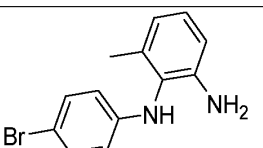
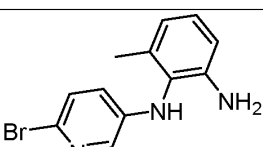
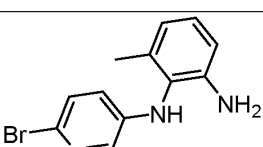
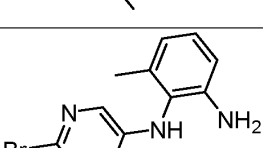
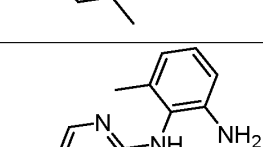
Intermediate number	Intermediate structure	LC-MS
Intermediate i-2 Route 1, Step A: 4-Bromo-2-methylaniline and 2-fluoro-1-methyl-3-nitro- benzene		Method 3: 4.60 min, m/z 321.1 / 323.1 [M] ⁺ / [M+2] ⁺
Intermediate i-3 Route 1, Step A: 1-fluoro-2-nitrobenzene and 4-bromo-2-methylaniline		¹ H NMR (400 MHz, DMSO-d ₆) δ 9.27 (s, 1H), 8.16 (d, J = 8.8 Hz, 1H), 7.64 (s, 1H), 7.57 – 7.44 (m, 2H), 6.93 – 6.84 (m, 1H), 7.28 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 8.7 Hz, 1H), 2.21 (s, 3H) ppm
Intermediate i-4 Route 1, Step A: 2-fluoro-1-methyl-3- nitrobenzene and 2-bromo-5-aminopyrimidine		Method 3: 1.84 min, m/z 309 [M] ⁺
Intermediate i-5 Route 1, Step A: 2-fluoro-1-methyl-3- nitrobenzene and 2-amino-5-bromopyrimidine		Method 4: 2.02 min, m/z 309.1 [M] ⁺
Intermediate i-6 Route 1, Step A: 2-fluoro-1-methyl-3- nitrobenzene and 3-amino-6-bromopyridazine		Method 3: 3.55 min, m/z 309.1 [M] ⁺
Intermediate i-7 Route 1, Step A: 2-fluoro-1-methyl-3- nitrobenzene and 2-amino-5-bromopyrazine		Method 2: 1.75 min, m/z 308.9 / 310.9 [M] ⁺ / [M+2] ⁺
Intermediate i-8 Route 1, Step A: 2-fluoro-1-methyl-3-nitro- benzene and 4-Bromoaniline		Method 4: 2.57 min, m/z, 307.0 [M] ⁺ .

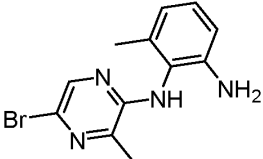
Intermediate i-9 Route 1, Step A: 2-fluoro-1-methyl-3-nitro- benzene and 5-Amino-2- bromopyridine		Method 3: 3.82 min, m/z, 310.2 [M+2] ⁺ .
Intermediate i-10 Route 5, Step A: 2-fluoro-1-methyl-3-nitro- benzene and 6-bromo-2-methyl- pyridin-3-amine		Method 4: 1.84 min, m/z 324.0, [M+2] ⁺
Intermediate i-11 Route 5, Step A: 2-fluoro-1-methyl-3-nitro- benzene and 6-bromo-4-methyl- pyridin-3-amine		Method 3: 4.05 min, m/z, 324.2 [M+2] ⁺
Intermediate i-12 Route 3, Step A: 2-fluoro-1-methyl-3-nitro- benzene and 2-Amino-5-bromo-3- methylpyridine		Method 3: 4.15 min, m/z, 324.1 [M+2] ⁺
Intermediate i-13 Route 1, Step A: 2-fluoro-1-methyl-3-nitro- benzene and 5-bromo-3-methyl-pyrazin- 2-amine		Method 3: 3.88 min, m/z, 323.2 [M] ⁺

Intermediates synthesised following the same procedure as intermediate **ii-1** (Route 1) replacing 5-bromo-N-(2-methyl-6-nitro-phenyl)pyridin-2-amine in Step B for the described intermediate are described in Table 4.

5 **Table 4.**

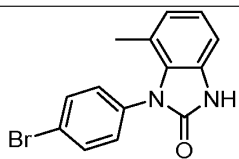
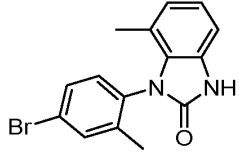
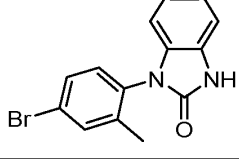
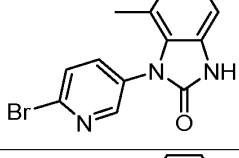
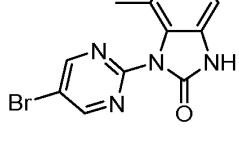
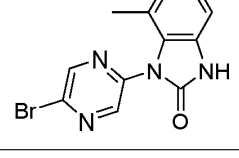
Intermediate number	Intermediate structure	LC-MS
Intermediate ii-2 Route 1, Step B		Method 3: 4.22 min, m/z 293.15 [M+2] ⁺

Intermediate ii-3 Route 1, Step B		Method 3: 4.35 min, m/z 277.0 [M] ⁺
Intermediate ii-4 Route 1, Step B		Method 4: 1.30 min, m/z 279.0 [M] ⁺
Intermediate ii-5 Route 1, Step B		Method 3: 2.95 min, m/z 279.1 [M] ⁺
Intermediate ii-6 Route 1, Step B		Method 2: 1.48 min, m/z 278.9 / 280.9 [M] ⁺ / [M+2] ⁺
Intermediate ii-7 Route 1, Step B		Method 4: 2.42 min, m/z, 277.0 [M] ⁺
Intermediate ii-8 Route 1, Step B		Method 3: 3.42 min, m/z, 278.2 [M] ⁺
Intermediate ii-9 Route 1, Step B		Method 4: 1.97 min, m/z 292.1 [M] ⁺
Intermediate ii-10 Route 1, Step B		Method 3: 3.52min, m/z, 292.2 [M] ⁺
Intermediate ii-11 Route 1, Step B		Method 3: 2.56 min, m/z, 292.2 [M] ⁺

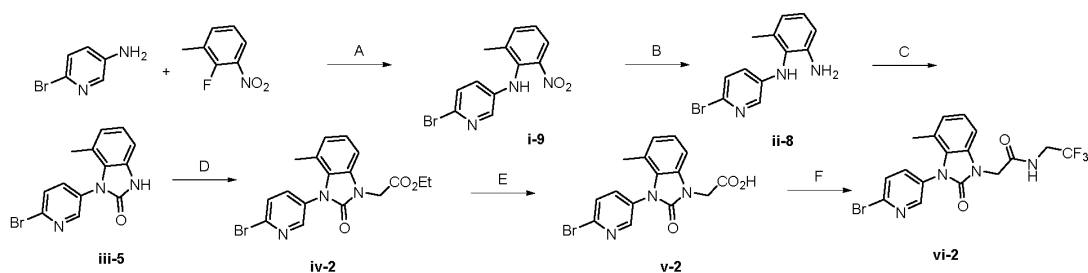
Intermediate ii-12 Route 1, Step B		Method 3: 3.05 min, m/z, 293.2 [M] ⁺
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Intermediates synthesised following the same procedure as intermediate **iii-1** (Route 1) replacing N2-(5-bromo-2-pyridyl)-3-methyl-benzene-1,2-diamine in Step C for the described building blocks are described in Table 5.

5 **Table 5.**

Intermediate number	Intermediate structure	LC-MS
Intermediate iii-2 Route 1, Step C		Method 3: 3.92 min, m/z 303.0 [M] ⁺
Intermediate iii-3 Route 1, Step C:		Method 3: 2.47 min, m/z 317.1 [M] ⁺
Intermediate iii-4 Route 1, Step C		Method 3: 3.98 min, m/z, 303.0 [M] ⁺
Intermediate iii-5 Route 1, Step C		Method 2: 1.51 min, m/z 304.0 / 305.9 [M] ⁺ / [M+2] ⁺
Intermediate iii-6 Route 1, Step C		Method 4: 1.03 min, m/z 305.0 [M] ⁺
Intermediate iii-7 Route 1, Step C		Method 2: 1.58 min, m/z 304.9 / 306.9 [M] ⁺ / [M+2] ⁺

Intermediate iii-8		Method 3: 3.35 min, m/z 307.1 [M+2] ⁺
Route 1, Step C		
Intermediate iii-9		Method 4: 1.60 min, m/z, 318.0 [M] ⁺
Route 1, Step C		
Intermediate iii-10		Method 3: 3.32 min, m/z, 318.1 [M] ⁺
Route 5, Step C		
Intermediate iii-11		Method 3: 2.47min, m/z, 317.1 [M+2] ⁺
Route 3, Step C		
Intermediate iii-12		Method 3: 3.38 min, m/z, 321.2 [M] ⁺
Route 1, Step C		

Route 2

Step A: Synthesis of **i-9**: Sodium hydride (420 mg, 17.34 mmol, 60% dispersion in mineral oil) was added in 100 mg portions to a stirring solution of 5-amino-2-bromopyridine (2.00 g, 11.56 mmol) at room temperature under a nitrogen atmosphere. 20 minutes after addition was complete, 2-fluoro-3-nitrotoluene (1.97 g, 12.72 mmol) was added. The reaction mixture was heated to 50 °C and left to stir overnight. The reaction was left to cool to room temperature and poured into water, EtOAc was added and the layers separated. The aqueous layer was extracted with further EtOAc twice. Organic fractions were collected, passed through phase separating filter paper and the solvent reduced in vacuo to afford the crude product. The crude material was purified by flash column chromatography eluting with 0-100% EtOAc in Pet. ether to afford the desired product 6-bromo-N-(2-methyl-6-nitro-phenyl)pyridin-3-amine (2.80 g, 9.09 mmol, 79% yield) as a dark orange oil.

UPLC-MS (ES⁺, Method 2): 1.78 min, m/z 307.9 / 309.9 [M]⁺ / [M+2]⁺

Step B: Synthesis of **ii-8**: Iron (5.89 g, 105.47 mmol) was added to a stirred mixture of 6-bromo-N-(2-methyl-6-nitro-phenyl)pyridin-3-amine (6.50 g, 21.09 mmol), ammonium chloride (5.64 g, 105.47 mmol), Ethanol (50 mL) and Water (10 mL) at room temperature. The reaction was heated to 75 °C and stirred for 30 minutes. The reaction was cooled to room temperature and filtered through a PTFE cartridge. The filtrate was concentrated in vacuo and then partitioned between water (100 mL) and DCM (100 mL). The organic layer was separated and the aqueous extracted with DCM (100 mL). The combined organic layers were dried over sodium sulfate and solvent removed in vacuo to give N2-(6-bromo-3-pyridyl)-3-methyl-benzene-1,2-diamine (4.50 g, 16.18 mmol, 77% yield) as a brown solid which was used in the next step without further purification. **UPLC-MS** (ES⁺, Method 2): 1.48 min, m/z 278.9 / 280.9 [M]⁺ / [M+2]⁺. **¹H NMR** (400 MHz, CDCl₃) δ 8.14 (d, J = 1.2 Hz, 1H), 7.41 (d, J = 1.2 Hz, 1H), 7.13 – 7.01 (m, 2H), 6.68 (d, J = 7.2 Hz, 1H), 5.92 (br s, 1H), 3.85 (br s, 2H), 2.17 (s, 3H) ppm.

Step C: Synthesis of **iii-5**: 1,1'-Carbonyldiimidazole (13.12 g, 80.89 mmol) as added to a stirring solution of N2-(6-bromo-3-pyridyl)-3-methyl-benzene-1,2-diamine (4.5 g, 16.18 mmol) in DMF (50 mL) at room temperature. The reaction was heated to 70 °C and stirred for 30 minutes. The reaction was cooled to room temperature and solvent removed in vacuo. Water was added to the residue, a solid precipitating. The solids were collected via filtration, washing with copious amounts of water and left to dry overnight to afford the desired product 3-(5-bromo-2-pyridyl)-4-methyl-1H-benzimidazol-2-one (2.8 g, 9.21 mmol, 80% yield) as a dark brown solid. **UPLC-MS** (ES⁺, Method 2): 1.51 min, m/z 304.0 / 305.9 [M]⁺ / [M+2]⁺. **¹H NMR** (400 MHz, DMSO-d₆) δ 11.21 (br s, 1H), 8.51 (dd, J = 2.7, 0.6 Hz, 1H), 7.92 (dd, J = 8.4, 2.7 Hz, 1H), 7.83 (dd, J = 8.4, 0.6 Hz, 1H), 7.01 – 6.91 (m, 2H), 6.82 – 6.77 (m, 1H), 1.84 (s, 3H) ppm.

Step D: Synthesis of **iv-2**: Ethyl bromoacetate (2.41 mL, 21.7 mmol) was added to a stirring solution of 3-(6-bromo-3-pyridyl)-4-methyl-1H-benzimidazol-2-one (4.40 g, 14.47 mmol) and cesium Carbonate (9.43 g, 28.93 mmol) in MeCN (50 mL). The reaction mixture was heated to 50 °C and left to stir for 24 hours. The reaction mixture was left to cool to room temperature before water and EtOAc were added and the layers separated. The aqueous layer was extracted with further EtOAc. Organic fractions were collected, passed through phase separating filter paper and the solvent reduced in vacuo to afford the crude product as a dark brown oil. The crude material was purified by flash column chromatography eluting with 0–100% EtOAc in Pet. Ether to afford the desired product ethyl 2-[3-(6-bromo-3-pyridyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetate (5.50 g, 14.09 mmol, 97% yield) as a light brown solid. **UPLC-MS** (ES⁺, Method 2): 1.73 min, m/z 390.1 / 392.0 [M]⁺ / [M+2]⁺. **¹H NMR** (400 MHz, DMSO-d₆) δ 8.56 (dd, J = 2.7, 0.6 Hz, 1H), 7.94 (dd, J = 8.4, 2.7 Hz, 1H), 7.86 (dd, J = 8.4, 0.6 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 7.01 – 7.03 (m, 1H), 6.89 (d, J = 7.4 Hz, 1H), 4.78 (s, 2H), 4.18 (q, J = 7.1 Hz, 2H), 1.87 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H) ppm.

Step E: Synthesis of **v-2**: Ethyl 2-[3-(6-bromo-3-pyridyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetate (5.50 g, 14.09 mmol) was stirred in sodium hydroxide (38.19 mL, 38.19 mmol) (1M) and THF (50 mL) at room temperature for 30 minutes. The reaction mixture was then acidified to ~pH5 using conc. HCl. EtOAc was added and the layers separated. The aqueous layer was extracted with further EtOAc. Organic fractions were collected, passed through phase separating filter paper and the solvent reduced in vacuo to afford the crude product 2-[3-(6-bromo-3-pyridyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetic acid (4.50

g, 12.43 mmol, 88% yield) as a grey solid. Material taken onto the next stage without any further purification. **UPLC-MS** (ES⁺, Method 2): 1.74 min, m/z 362.0 / 364.0 [M]⁺ / [M+2]⁺

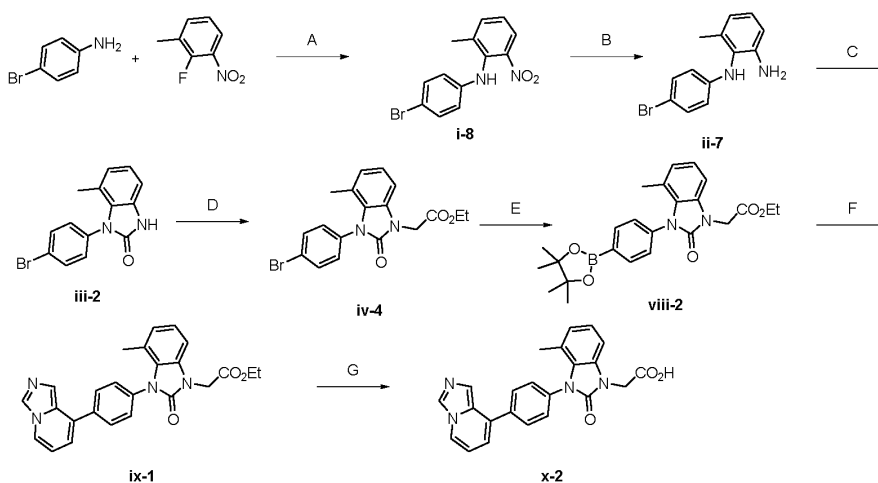
¹H NMR (400 MHz, DMSO-d₆) δ 13.08 (br s, 1H), 8.56 (dd, J = 2.7, 0.6 Hz, 1H), 7.93 (dd, J = 8.4, 2.7 Hz, 1H), 7.85 (dd, J = 8.4, 0.6 Hz, 1H), 7.13 (d, J = 7.4 Hz, 1H), 7.09 - 7.03 (m, 1H), 6.88 (d, J = 7.4 Hz, 1H), 4.67 (s, 2H), 1.87 (s, 3H) ppm.

Step F: Synthesis of **vi-2**: HATU (3.15 g, 8.28 mmol) was added to a stirring solution of 2-[3-(6-bromo-3-pyridyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetic acid (2.50 g, 6.9 mmol), N,N-diisopropylethylamine (2.4 mL, 13.81 mmol) and trifluoroethylamine (0.82 mL, 10.35 mmol) in DMF (20 mL). The reaction mixture was left to stir at room temperature for 30 min. The reaction mixture was poured into water, a solid precipitating. The solids were collected via filtration, washing with water and left to dry overnight. The desired product 2-[3-(6-bromo-3-pyridyl)-4-methyl-2-oxo-benzimidazol-1-yl]-N-(2,2,2-trifluoroethyl)acetamide (2.80 g, 6.32 mmol, 92% yield) was afforded as a pale yellow solid.

UPLC-MS (ES⁺, Method 2): 1.89 min, m/z 443.0 / 445.0 [M]⁺ / [M+2]⁺

¹H NMR (400 MHz, DMSO-d₆) δ 8.90 (d, J = 8.8, 1H), 8.78 (dd, J = 2.6, 0.5 Hz, 1H), 8.31 (dd, J = 8.5, 2.6 Hz, 1H), 7.63 (dd, J = 8.4, 0.4 Hz, 1H), 7.08 - 7.02 (m, 1H), 6.97 (d, J = 7.4 Hz, 1H), 6.88 (d, J = 7.5 Hz, 1H), 4.67 - 4.53 (m, 3H), 1.86 (s, 3H), 1.28 (d, J = 7.0 Hz, 3H) ppm.

Route 3



Step A: Synthesis of **i-8**: To a solution of 4-bromoaniline (30.00 g, 174.40 mmol, 1.0 eq) in DMF (120 mL) under N₂ at 0 °C was slowly added NaH (10.50 g, 261.60 mmol, 1.5 eq, 60 % dispersion in mineral oil). The reaction mixture was stirred at 0 °C for 0.5 h. 2-Fluoro-1-methyl-3-nitrobenzene (32.50 g, 209.20 mmol, 1.2 eq) in DMF (80 mL) was added slowly and the reaction mixture was stirred at rt overnight. The reaction mixture was diluted with water (2000 mL) and extracted with EtOAc (600 mL x 5). The combined organic layers were dried over Na₂SO₄, concentrated under vacuum and purified by silica gel chromatography (Pet.ether~Pet.ether/ EtOAc 30:1, v/v) to provide N-(4-bromophenyl)-2-methyl-6-nitro-aniline (12.80 g, 24%) as red solid. **UPLC-MS** (ES⁺, Method 3): 4.58 min, m/z 307.0 [M+H]⁺

Step B: Synthesis of **ii-7**: To a solution of N-(4-bromophenyl)-2-methyl-6-nitro-aniline (12.80 g, 41.67 mmol, 1.0 eq) in ethanol/water (150 mL, 2:1, v/v) under N₂ at rt was added iron (11.67 g, 208.37 mmol, 5.0 eq) and NH₄Cl (11.15 g, 208.37 mmol, 5.0 eq). The reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was filtered and diluted with water (300 mL). The aqueous layer was separated and extracted with EtOAc (300 mL x 3). The combined organic layers were washed by brine (300 mL), dried over Na₂SO₄ and concentrated under vacuum to provide N2-(4-bromophenyl)-3-methyl-benzene-1,2-diamine (10.40 g, 90%) as a yellow solid. **UPLC-MS (ES⁺, Method 4):** 2.42 min, m/z 277.0 [M+H]⁺

Step C: Synthesis of **iii-2**: To a solution of N2-(4-bromophenyl)-3-methyl-benzene-1,2-diamine (10.4 g, 37.5 mmol, 1.0 eq) in DMF (60 mL) under N₂ was slowly added CDI (18.2 g, 112.6 mmol, 3.0 eq) at 0 °C. The reaction mixture was stirred at 100 °C overnight. The mixture was diluted with water (700 mL) and extracted with EtOAc (300 mL x 3). The combined organic layers were washed with brine (400 mL), dried over Na₂SO₄ and concentrated under vacuum to afford 3-(4-bromophenyl)-4-methyl-1H-benzimidazol-2-one (9.20 g, 81%) as a yellow solid.

UPLC-MS (ES⁺, Method 4): 2.06 min, m/z 303.0 / 305.0 [M+]⁺ / [M+2]⁺

Step D: Synthesis of **iv-4**: A solution of 3-(4-bromophenyl)-4-methyl-1H-benzimidazol-2-one (5.30 g, 17.48 mmol, 1.0 eq), ethyl bromoacetate (4.38 g, 26.23 mmol, 1.5 eq), and Cs₂CO₃ (11.39 g, 34.97 mmol, 2.0 eq) in MeCN (30 mL) was stirred at 50 °C for 2h. The reaction mixture was quenched with H₂O (50 mL). The aqueous layer was separated and extracted with EtOAc (50 mL x 3). The organic layers were combined, washed with H₂O (250 mL x 3), brine (50 mL x 3), and dried over Na₂SO₄. The mixture was concentrated under vacuum and purified by silica gel column (Pet. ether/EtOAc=20/1~ Pet. ether/EtOAc=3/1, v/v) to give ethyl 2-[3-(4-bromophenyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetate (5.30 g, 78%) as a white solid. **UPLC-MS (ES⁺, Method 3):** 4.28 min, m/z 389.0 / 391.0 [M]⁺ / [M+2]⁺

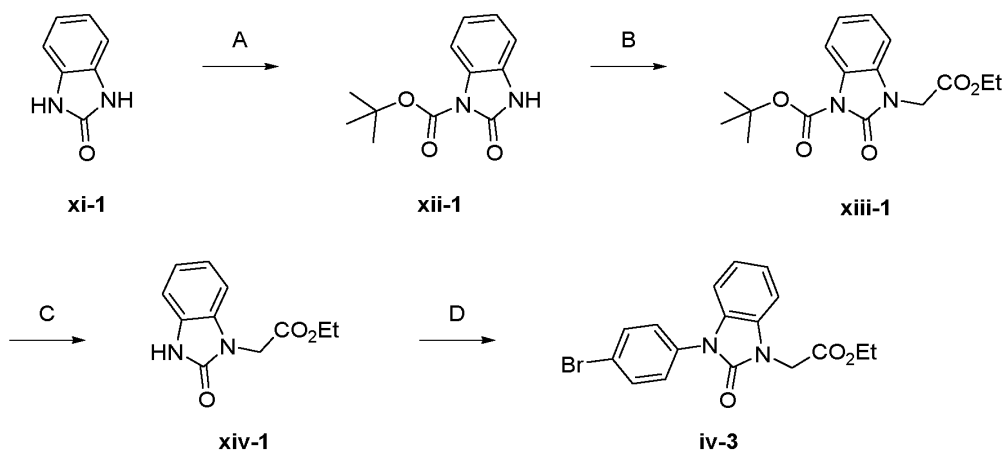
Step E: Synthesis of **viii-2**: To a solution of ethyl 2-(3-(4-bromophenyl)-4-fluoro-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)acetate (1.00 g, 2.27 mmol, 1.0 eq) in THF (5 mL) under a N₂ atmosphere was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (864 mg, 3.40 mmol, 2.0 eq), Pd₂(dba)₃ (208 mg, 0.227 mmol, 0.2 eq), X-phos (216 mg, 0.453 mmol, 0.2 eq) and KOAc (668 mg, 6.80 mmol, 3.0 eq). The reaction mixture was heated at 70 °C for 16h. The mixture was cooled to rt, diluted with water (10 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with water (20 mL x 3), brine (20 mL x 3), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column (Pet. ether/EtOAc 20:1 – Pet ether/EtOAc 3:1) to afford ethyl 2-[4-methyl-2-oxo-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]benzimidazol-1-yl]acetate (1.04 g, 90%) as a brown solid. **UPLC-MS (ES⁺, Method 3):** 4.58 min, m/z 437.0 [M]⁺

Step F: Synthesis of **ix-1**: A solution of ethyl 2-[4-methyl-2-oxo-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]benzimidazol-1-yl]acetate (400 mg, 0.917 mmol, 1.0 eq), 8-bromoimidazo[1,5-a]pyridine (199 mg, 1.01 mmol, 1.1 eq), K₂CO₃ (254 mg, 1.83 mmol, 2.0 eq), and Pd(dppf)Cl₂ (74 mg, 0.092 mmol, 0.1 eq), in DMF (5.0 mL) was stirred at 90 °C under N₂ overnight. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (10 mL x 3). The organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated to give of yellow solid. The mixture was purified by P-TLC to afford ethyl 2-[3-(4-imidazo[1,5-a]pyridin-8-ylphenyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetate (290 mg, 74%) as a yellow solid.

UPLC-MS (ES⁺, Method 3): 3.15 min, m/z 427.0 [M]⁺

Step G: Synthesis of **x-2**: A solution of ethyl 2-[3-(4-imidazo[1,5-a]pyridin-8-ylphenyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetate (290 mg, 0.68 mmol, 1.0 eq), and LiOH.H₂O (85.6 mg, 2.04 mmol, 5.0 eq) in THF (3 mL), MeOH (3 mL) and H₂O (2 mL) was stirred at 25°C for 2h. The reaction mixture was diluted with H₂O (5 mL) and 10% HCl (8 mL) to pH 2 / 3. The mixture was diluted with water (20 mL x 3) and extracted with DCM (20 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo to obtain ethyl 2-[3-(4-imidazo[1,5-a]pyridin-8-ylphenyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetate (280 mg, 49%). **UPLC-MS** (ES⁺, Method 3): 2.75 min, m/z 399.0 [M]⁺

Route 4



Step A: Synthesis of **xii-1**: To a solution of 2-hydroxybenzimidazole (500 mg, 3.73 mmol) in DMF (10mL) was added sodium hydride (150 mg, 3.75 mmol, 60% dispersion in mineral oil) and the reaction mixture was stirred at room temperature for 1.5 hours. A solution of di-tert-butyl dicarbonate (814 mg, 3.73 mmol) in DMF (5mL) was added dropwise. The reaction mixture was stirred at room temperature for 4 hours then was evaporated to dryness. The residue was diluted with ethyl acetate and sat. aq. NH₄Cl. The phases were separated and the aqueous phase was extracted with ethyl acetate. The organic phases were washed with brine then passed through phase separator filter paper and evaporated to dryness to afford tert-butyl 2-oxo-3H-benzimidazole-1-carboxylate (870 mg, 3.71 mmol, 100% yield) as an off-white solid. **UPLCMS** (ES⁺, Method 2): 1.55 min, m/z 233.1 [M]⁺

Step B: Synthesis of **xiii-1**: A mixture of cesium carbonate (181 mg, 0.55 mmol), ethyl bromoacetate (0.05 mL, 0.47 mmol) and tert-butyl 2-oxo-3H-benzimidazole-1-carboxylate (100 mg, 0.43mmol) in MeCN (2.5 mL) was heated at 80 °C for 2 hours. The reaction mixture was evaporated to dryness and the residue was suspended in water. The aqueous phase was extracted with ethyl acetate four times. The organic phases were washed with brine, passed through phase separator filter paper and evaporated to dryness. The residue was purified by flash column chromatography (4 g cartridge, eluent ethyl acetate in petroleum ether 0-25%) to afford tert-butyl 3-(2-ethoxy-2-oxo-ethyl)-2-oxo-benzimidazole-1-carboxylate (100 mg, 0.31 mmol, 73% yield) as a colourless oil.

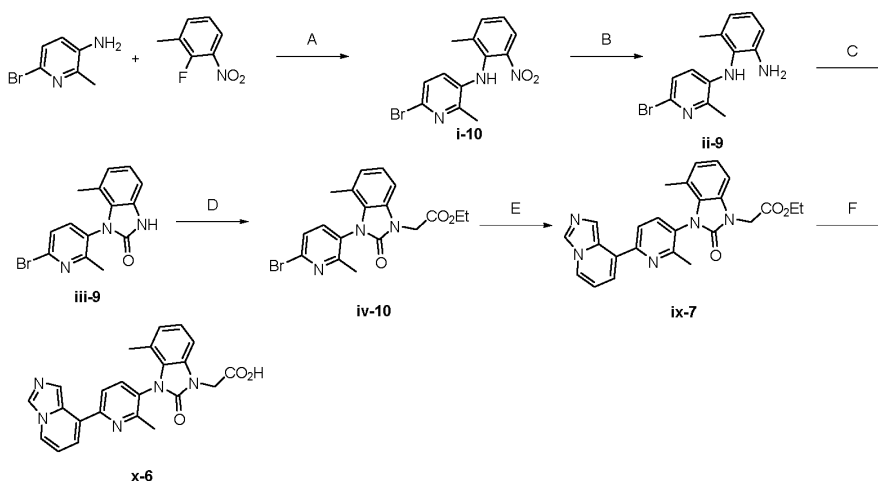
UPLCMS (ES⁺, Method 2): 1.79 min, m/z 343.0 [M+Na]⁺

Step C: Synthesis of **xiv-1**: Tert-butyl 3-(2-ethoxy-2-oxo-ethyl)-2-oxo-benzimidazole-1-carboxylate (1.14g, 3.56 mmol) was dissolved in DCM (25 mL) and trifluoroacetic acid (2.73 mL, 35.59 mmol) was

added. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was evaporated to dryness, co-evaporated with toluene to afford ethyl 2-(2-oxo-3H-benzimidazol-1-yl)acetate (700 mg, 3.18 mmol, 89% yield) as a white solid. **UPLCMS** (ES⁺, Method 2): 1.32 min, m/z 221.1 [M+H]⁺. **¹H NMR** (400 MHz, DMSO-d₆) δ 10.95 (s, 1H), 7.11 - 7.07 (m, 1H), 7.01 - 7.00 (m, 3H), 4.66 (s, 2H), 4.15 (q, J = 7.1 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H) ppm.

Step D: Synthesis of **iv-3**: 4-Bromo-benzeneboronic acid (911 mg, 4.54 mmol), ethyl 2-(2-oxo-3H-benzimidazol-1-yl)acetate (500 mg, 2.27 mmol) and copper(II) acetate (824 mg, 4.54 mmol) were mixed in DCM (15mL) and Triethylamine (0.95 mL, 6.81mmol) was added. The reaction mixture was stirred in open air at room temperature overnight. The reaction mixture was diluted with dichloromethane and water. The phases were separated and the aqueous phase was extracted with dichloromethane. The organic phases were washed with brine, passed through phase separator and evaporated to dryness. The residue was purified by flash column chromatography eluting with EtOAc in Pet.ether (0-25%) to afford ethyl 2-[3-(4-bromophenyl)-2-oxo-benzimidazol-1-yl]acetate (364 mg, 0.97 mmol, 43% yield) as a white solid. **UPLCMS** (ES⁺, Method 2): 1.88 min, m/z 375.0 / 377.0 [M]⁺ / [M+2]⁺

15 Route 5



Step A: Synthesis of **i-10**: To a solution of 6-bromo-2-methyl-pyridin-3-amine (5.00 g, 26.7 mmol) in DMF (100 mL) was added NaH (1.60 g, 40.1 mmol) slowly at 0 °C and stirred at 0 °C under N₂ for 30 mins. Then 2-fluoro-1-methyl-3-nitro-benzene (4.15 g, 26.7 mmol) was added to the mixture and stirred at 30 °C under N₂ overnight. The mixture was diluted with water (200 mL) and extracted with EtOAc (100 mL x 3). The combined organic extracts were washed with water (500 mL x 2), brine (500 mL), dried over Na₂SO₄ and concentrated in vacuum. The crude was purified by column chromatography on silica gel (Pet.ether/EtOAc=30/1, v/v) to afford 6-bromo-2-methyl-N-(2-methyl-6-nitro-phenyl)pyridin-3-amine (4.00 g, 12.4 mmol, 46% yield). LC-MS (ES-API, Method 4): 1.84 min, 322.0/324.0 m/z, [M]⁺. **¹H NMR** (400 MHz, DMSO-d₆) δ 7.83 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 7.5 Hz, 1H), 7.54 (s, 1H), 7.40-7.34 (m, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.44 (d, J = 8.4 Hz, 1H), 2.43 (s, 3H), 2.13 (s, 3H) ppm.

Step B: Synthesis of **ii-9**: A mixture of 6-bromo-2-methyl-N-(2-methyl-6-nitro-phenyl)pyridin-3-amine (4.75 g, 14.7 mmol) Fe (4.12 g, 73.7 mmol) and NH₄Cl (7.89 g, 147 mmol) in Ethanol (120 mL) and

Water (40 mL) were stirred at 80 °C for 1h. The mixture was filtered and concentrated in vacuum to give the crude. The crude was washed with water (100 mL) and extracted with EtOAc (50 mL x 3). The combined organic extracts were washed with brine (200 mL), dried over Na₂SO₄ and concentrated in vacuum to give N₂-(6-bromo-2-methyl-3-pyridyl)-3-methyl-benzene-1,2-diamine (4.20 g, 14.4 mmol, 97% yield) as a yellow solid. LC-MS (ES-API, Method 4): 1.37 min, 292.0/294.0 m/z, [M]⁺. **¹H NMR** (400 MHz, DMSO-d₆) δ 7.07 (d, *J* = 8.4 Hz, 1H), 6.94 – 6.87 (m, 1H), 6.67 (s, 1H), 6.62 (d, *J* = 7.9 Hz, 1H), 6.47 (d, *J* = 7.3 Hz, 1H), 6.14 (d, *J* = 8.5 Hz, 1H), 4.84 (s, 2H), 2.46 (s, 3H), 1.99 (s, 3H) ppm.

Step C: Synthesis of **iii-9**: A mixture of N₂-(6-bromo-2-methyl-3-pyridyl)-3-methyl-benzene-1,2-diamine (3.69 g, 12.6 mmol) and CDI (6.14 g, 37.9 mmol) in DMF (50 mL) were stirred at 100 °C under N₂ for 2h. The mixture was diluted with water (500 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with water (1 L), brine (1 L), dried over Na₂SO₄ and concentrated in vacuum. The crude material was purified by flash column chromatography on silica gel (DCM/MeOH=100/1, v/v) to give 3-(6-bromo-2-methyl-3-pyridyl)-4-methyl-1H-benzimidazol-2-one (4.10 g, 12.9 mmol, quantitative yield) as a yellow solid. LC-MS (ES-API, Method 4): 1.16 min, m/z, 318.0/320.0 [M]⁺. **¹H NMR** (400 MHz, DMSO-d₆) δ 11.90 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.00 – 6.93 (m, 2H), 6.80 – 6.75 (m, 1H), 2.25 (s, 3H), 1.74 (s, 3H) ppm.

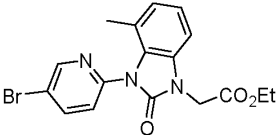
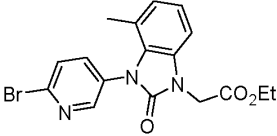
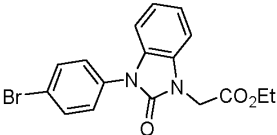
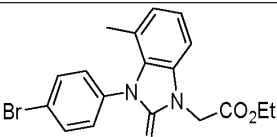
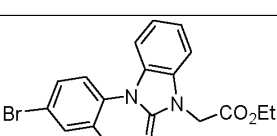
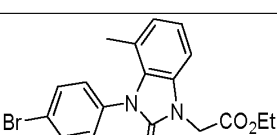
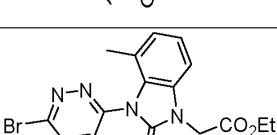
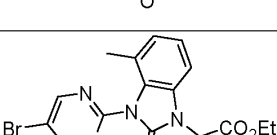
Step D: Synthesis of **iv-10**: A mixture of 3-(6-bromo-2-methyl-3-pyridyl)-4-methyl-1H-benzimidazol-2-one (4.10 g, 12.9 mmol) Ethyl bromoacetate (2.14 mL, 19.3 mmol) and Cs₂CO₃ (8.40 g, 25.8 mmol) in MeCN (50 mL) were stirred at 25 °C overnight. The mixture was filtered and concentrated in vacuum. The crude material was purified by flash column chromatography on silica gel (Pet.ether/EtOAc = 2/1, v/v) to give ethyl 2-[3-(6-bromo-2-methyl-3-pyridyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetate (4.98 g, 12.3 mmol, 96% yield) as a yellow solid. LC-MS (ES-API, Method 4): 2.19 min, m/z, 404.0/406.0 [M]⁺. **¹H NMR** (400 MHz, DMSO-d₆) δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.08 – 7.02 (m, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 4.88 – 4.73 (m, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.24 (s, 3H), 1.78 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H) ppm.

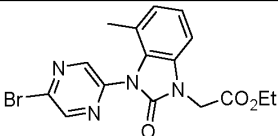
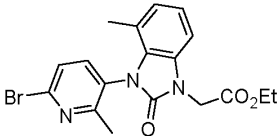
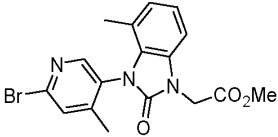
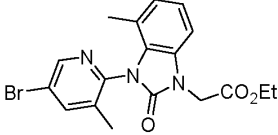
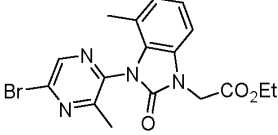
Step E: Synthesis of **ix-7**: A mixture of ethyl 2-[3-(6-bromo-2-methyl-3-pyridyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetate (586 mg, 1.45 mmol), CuI (138 mg, 0.720 mmol), LiCl (184 mg, 4.35 mmol), tributyl(imidazo[1,5-a]pyridine-8-yl)stannane (708 mg, 1.74 mmol) and Pd(PPh₃)₄ (168 mg, 0.140 mmol) in *m*-Xylene (10 mL) were stirred at 130 °C under N₂ overnight. The mixture was concentrated in vacuum. The crude material was purified by flash column chromatography on silica gel (DCM/MeOH=50/1, v/v) to give ethyl 2-[3-(6-imidazo[1,5-a]pyridine-8-yl-2-methyl-3-pyridyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetate (588 mg, 1.33 mmol, 92% yield) as a brown solid. LC-MS (ES-API, Method 4): 1.24 min, m/z, 442.2 [M]⁺

Step F: Synthesis of **x-6**: A mixture of ethyl 2-[3-(6-imidazo[1,5-a]pyridine-8-yl-2-methyl-3-pyridyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetate (588 mg, 1.33 mmol) and LiOH.H₂O (168 mg, 4.00 mmol) in THF (5 mL) and Water (5 mL) were stirred at 25 °C for 1h. The reaction mixture was adjusted to pH 3 and filtrated, the filter cake was concentrated in vacuum to give 2-[3-(6-imidazo[1,5-a]pyridine-8-yl-2-methyl-3-pyridyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetic acid (383 mg, 0.930 mmol, 70% yield) as a yellow solid. LC-MS (ES-API, Method 4): 0.82 min, m/z, 414.2 [M]⁺

Intermediates synthesised following the same procedure as Intermediate **iv-1** (Route 1) replacing 3-(5-bromo-2-pyridyl)-4-methyl-1H-benzimidazol-2-one in Step D for the described building block and **iv-4** (Route 4) replacing ethyl 2-(2-oxo-3H-benzimidazol-1-yl)acetate in Step D for the described building blocks are described in Table 6.

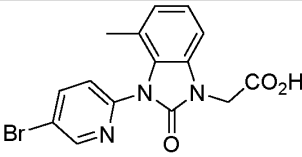
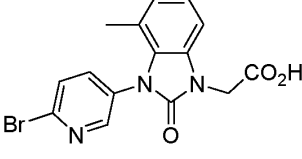
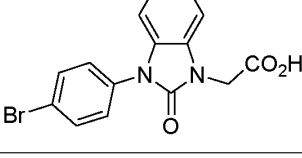
5 **Table 6.**

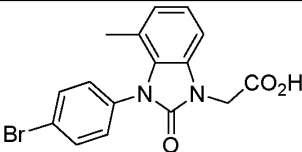
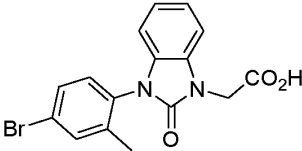
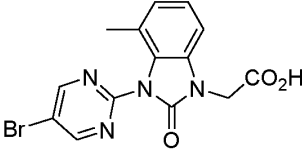
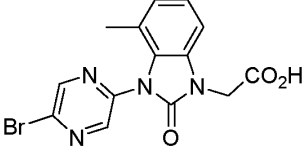
Intermediate number	Intermediate structure	LC-MS
Intermediate iv-1 Route 1, Step D		Method 3: 4.12 min, m/z 392.1 [M+2] ⁺
Intermediate iv-2 Route 2, Step D		Method 3: 3.98 min, m/z, 390.2 [M] ⁺
Intermediate iv-3 Route 4, Step D		Method 2: 1.88 min, m/z 375.0 / 377.0 [M] ⁺ / [M+2] ⁺
Intermediate iv-4 Route 1, Step D		Method 3: 4.28 min, m/z 389.0 [M] ⁺
Intermediate iv-5 Route 1, Step D		Method 3: 4.32 min, m/z 389.1 / 391.1 [M] ⁺ / [M+2] ⁺
Intermediate iv-6 Route 1, Step D		Method 3: 4.15 min, m/z 403.1 [M] ⁺
Intermediate iv-7 Route 1, Step D		Method 3: 3.85 min, m/z 391.1 [M] ⁺
Intermediate iv-8 Route 1, Step D		Method 4: 1.94 min, m/z 390.9 [M] ⁺

Intermediate iv-9 Route 1, Step D		Method 3: 4.07 min, m/z 391.0 [M] ⁺
Intermediate iv-10 Route 5, Step D		Method 4: 2.14 min, m/z, 404.0 [M] ⁺
Intermediate iv-11 Route 5, Step D		Method 3: 3.55 min, m/z, 392.2 [M+2] ⁺
Intermediate iv-12 Route 3, Step D		Method 3: 4.15 min, m/z, 403.1 [M] ⁺
Intermediate iv-13 Route 1, Step D		Method 3: 3.88 min, m/z, 407.2 [M+2] ⁺

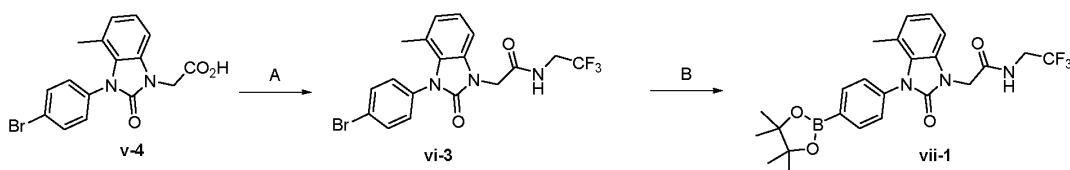
Intermediates synthesised following the same procedure as Intermediate **v-1** (Route 1) replacing ethyl 2-[3-(5-bromo-2-pyridyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetate in Step E for the described building block are described in Table 7.

Table 7.

Intermediate number	Intermediate structure	LC-MS
Intermediate v-1 Route 1, Step E:		Method 2: 1.71 min, m/z 362.0 / 364.0 [M] ⁺ / [M+2] ⁺
Intermediate v-2 Route 1, Step E		Method 2: 1.74min, m/z 362.0 / 364.0 [M] ⁺ / [M+2] ⁺
Intermediate v-3 Route 1, Step E:		Method 3: 3.92min, m/z, 349.0 [M+2] ⁺

Intermediate v-4 Route 1, Step E		Method 3: 3.98 min, m/z 361.0 [M] ⁺
Intermediate v-5 Route 1, Step E		Method 4: 2.19 min, m/z, 375.0 [M] ⁺
Intermediate v-6 Route 1, Step E		Method 3: 1.13 min, m/z 363.0 [M] ⁺
Intermediate v-7 Route 1, Step E		Method 2: 1.54 min, m/z 362.9 / 364.9 [M] ⁺ / [M+2] ⁺

Route 6

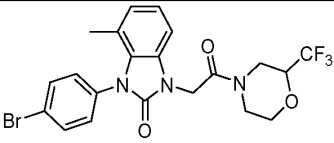
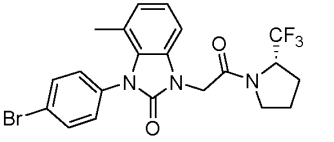
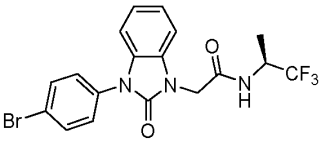


- Step A:** Synthesis of **vi-3**: 2-[3-(4-bromophenyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetic acid (15.8 mg, 43.74 mmol), trifluoroethylamine (6.5 g, 65.8 mmol), HATU (24.9 g, 65.62 mmol) and DIPEA (8.5 g, 65.62 mmol) in DMF (100 mL) was stirred at 25 °C for 16 h. The mixture was quenched with H₂O (100 mL) and the mixture was extracted with EtOAc (150 mL x 3). The organic layers were combined, washed with H₂O (150 mL x 3), then NaCl(aq.) (150 mL x 3), and the organic phase was dried over anhydrous Na₂SO₄. The mixture was concentrated in vacuum and purified by silica gel column (Pet.ether/EtOAc = 20/1→2/1) to give 2-[3-(4-bromophenyl)-4-methyl-2-oxo-benzimidazol-1-yl]-N-(2,2,2-trifluoroethyl)acetamide (19.3 g, 43.74 mmol, quantitative yield) as a white solid. Method 3: 4.08 min, m/z, 442.0 [M]⁺
- Step B:** Synthesis of **vii-1**: A solution of 2-[3-(4-bromophenyl)-4-methyl-2-oxo-benzimidazol-1-yl]-N-(2,2,2-trifluoroethyl)acetamide (2000 mg, 4.52 mmol), Bis(pinacolato)diboron (2296.8 mg, 9.04 mmol), Potassium Acetate (1331.6mg, 13.57 mmol), X-PHOS (431.2mg, 0.90 mmol), and Pd₂(dba)₃ (828.2 mg, 0.90 mmol) in THF (20 mL) was stirred at 70 °C under N₂ overnight. The mixture was concentrated in vacuum and purified by silica gel column (Pet.ether/EtOAc=10/1~ Pet.ether/EtOAc=1/1, v/v) to give 2-[4-methyl-2-oxo-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]benzimidazol-1-yl]-N-(2,2,2-trifluoroethyl)acetamide (2.2 g, 4.52 mmol, quantitative yield) as an off-white solid. Method 3: 4.37 min, m/z, 490.2 [M+H]⁺

Intermediates synthesised following the same procedure as Intermediate **vi-3** (Route 6) replacing 2-[3-(4-bromophenyl)-4-methyl-2-oxo-benzimidazol-1-yl]acetic acid and trifluoroethylamine in Step F for the described building block are described in Table 8.

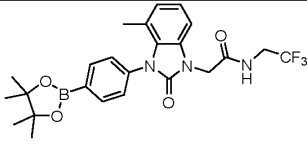
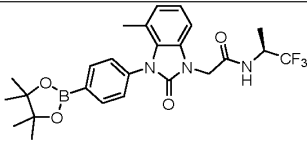
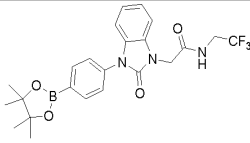
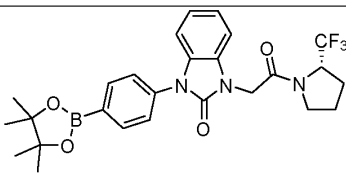
Table 8.

Intermediate number	Intermediate structure	LC-MS
Intermediate vi-1 Route 6, Step A		Method 2: 1.89 min, m/z 443.0 / 445.0 [M] ⁺ / [M+2] ⁺
Intermediate vi-2 Route 6, Step A		Method 3: 1.87 min, m/z, 429.9 [M+2] ⁺
Intermediate vi-3 Route 6, Step A		Method 3: 4.07 min, m/z 442.0 [M] ⁺
Intermediate vi-4 Route 6, Step A		Method 3: 4.28 min, m/z 458.10 [M+2] ⁺
Intermediate vi-5 Route 6, Step A		Method 2: 1.87 min, m/z 445.0 [M+2] ⁺
Intermediate vi-6 Route 6, Step A		Method 3: 1.30 min, m/z 444.0 [M] ⁺
Intermediate vi-7 Route 6, Step A		Method 4: 1.81 min, m/z 468.0 [M] ⁺
Intermediate vi-8 Route 6, Step A		Method 3: 4.15 min, m/z, 444.2 [M+2] ⁺

Intermediate vi-9 Route 6, Step A		Method 3: 4.25 min, m/z, 498.0 [M] ⁺
Intermediate vi-10 Route 6, Step A		Method 3: 4.35 min, m/z, 484.1 [M+2] ⁺
Intermediate vi-11 Route 6, Step A		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.89 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.7 Hz, 2H), 7.17 - 7.04 (m, 4H), 4.69-4.55 (m, 3H), 1.28 (d, J = 7.0 Hz, 3H)

Intermediates synthesised following the same procedure as Intermediate **vii-1** (Route 6) replacing 2-[3-(4-bromophenyl)-4-methyl-2-oxo-benzimidazol-1-yl]-N-(2,2,2-trifluoroethyl)acetamide in Step B for the described intermediates are also described in Table 9.

Table 9.

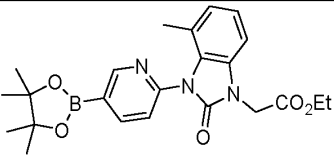
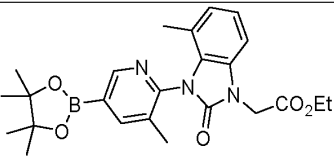
Intermediate number	Intermediate structure	LC-MS
Intermediate vii-1 Route 6, Step B		Method 3: 4.32 min, m/z 490.0 [M+H] ⁺
Intermediate vii-2 Route 6, Step B		Method 3: 4.48 min, m/z 504.2 [M+H] ⁺
Intermediate vii-3 Route 6, Step B		Method 2: 1.91 min, m/z 476.5 [M+H] ⁺
Intermediate vii-4 Route 6, Step B		Method 4: 2.18 min, m/z 516.2 [M+H] ⁺

Intermediate vii-5 Route 6, Step B		Method 3: 4.42 min, m/z 490.3 [M+H] ⁺
Intermediate vii-6 Route 6, Step B		Method 3: 4.48 min, m/z 546.3 [M+H] ⁺
Intermediate vii-7 Route 6, Step B		Method 3: 4.63 min, m/z 530.3 [M+H] ⁺
Intermediate vii-8 Route 6, Step B		¹ H NMR (400 MHz, DMSO-d ₆) δ 7.97-7.75 (m, 4H), 7.65-7.55 (m, 1H), 7.51-7.43 (m, 1H), 7.19-7.04 (m, 3H), 4.71-4.55 (m, 3H), 1.38-1.03 (m, 15H)

Intermediates synthesised following the same procedure as Intermediate **viii-1** (Route 3) replacing ethyl 2-(3-(4-bromophenyl)-4-fluoro-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)acetate in Step E for the described intermediates are described in Table 10.

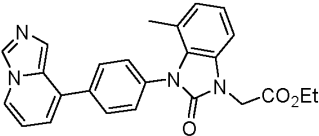
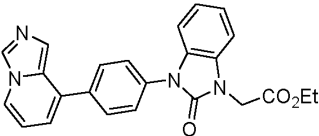
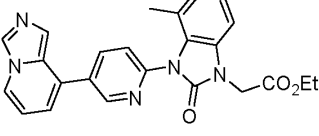
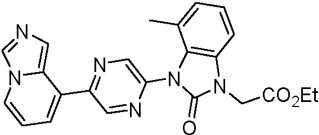
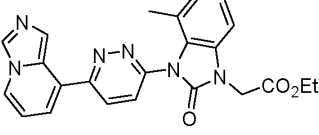
Table 10.

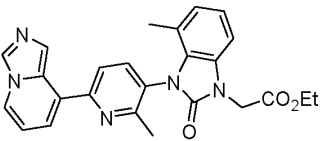
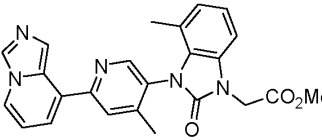
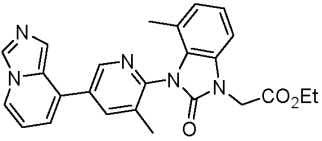
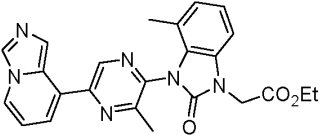
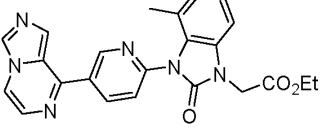
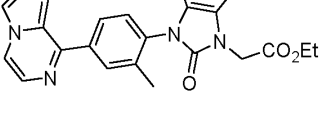
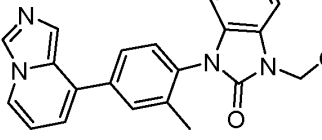
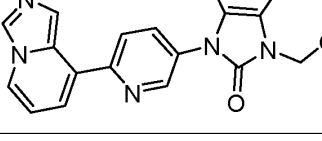
Intermediate number	Intermediate structure	LC-MS
Intermediate viii-1 Route 3, Step E		Method 3: 2.27 min, m/z 423.2 [M+H] ⁺
Intermediate viii-2 Route 3, Step E		Method 3: 4.62 min, m/z 437.0 [M+H] ⁺
Intermediate viii-3 Route 3, Step E		Method 3: 4.47 min, m/z 451.3 [M+H] ⁺

Intermediate viii-4 Route 3, Step E		Method 3: 4.18 min, m/z 438.3 [M+H] ⁺
Intermediate viii-5 Route 3, Step E		Method 3: 4.45min, m/z, 451.3 [M] ⁺

Intermediates synthesised following the same procedure as Intermediate **ix-1** (Route 3) replacing ethyl 2-[4-methyl-2-oxo-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]benzimidazol-1-yl]acetate and 8-bromo-imidazo[1,5-a]pyridine in Step F for the described building block are described in Table 11.

5 **Table 11.**

Intermediate number	Intermediate structure	LC-MS
Intermediate ix-1 . Route 3, Step F using Intermediate viii-2 and 8- bromo-imidazo[1,5-a]pyridine		Method 3: 3.15 min, m/z, 427.0 [M+H] ⁺
Intermediate ix-2 . Route 3, Step F using Intermediate viii-1 and 8- bromo-imidazo[1,5-a]pyridine		Method 3: 3.09 min, m/z 413.1 [M+H] ⁺
Intermediate ix-3 . Route 3, Step F using Intermediate viii-4 and 8- bromo-imidazo[1,5-a]pyridine		Method 3: 3.05 min, m/z 428.3 [M+H] ⁺
Intermediate ix-5 . Route 5, Step E using Intermediate iv-9 and tributyl(imidazo[1,5-a]pyridin-8- yl)stannane		Method 3: 2.82 min, m/z 429.3 [M+H] ⁺
Intermediate ix-6 Route 5, Step E using Intermediate iv-7 and tributyl(imidazo[1,5- a]pyridin-8-yl)stannane		Method 3: 2.82 min, m/z 429.25 [M+H] ⁺

Intermediate ix-7 Route 5, Step E using Intermediate iv-10 and tributyl(imidazo[1,5-a]pyridin-8-yl)stannane		Method 4: 1.24 min, m/z, 442.2 [M+H] ⁺
Intermediate ix-8 Route 5, Step E using Intermediate iv-11 and tributyl(imidazo[1,5-a]pyridin-8-yl)stannane		Method 3: 2.72 min, m/z, 428.3 [M+H] ⁺
Intermediate ix-9 Route 3, Step F using Intermediate viii-6 and 8-bromo-midazo[1,5-a]pyridine		Method 3: 3.35 min, m/z, 442.3 [M+H] ⁺
Intermediate ix-10 Route 5, Step E using Intermediate iv-13 and tributyl(imidazo[1,5-a]pyridin-8-yl)stannane		Method 3: 2.98 min, m/z, 443.4 [M+H] ⁺
Intermediate ix-11 Route 3, Step F using Intermediate viii-4 and 8-chloro-imidazo[1,5-a]pyrazine		Method 3: 3.16 min, m/z 429.2 [M+H] ⁺
Intermediate ix-12 Route 3, Step F using Intermediate viii-3 and 8-chloro-imidazo[1,5-a]pyrazine		Method 3: 3.34 min, m/z 442.2 [M+H] ⁺
Intermediate ix-14 Route 3, Step F using Intermediate viii-3 and 8-bromo-imidazo[1,5-a]pyridine		Method 3: 3.12 min, m/z 441.4 [M+H] ⁺
Intermediate ix-15 Route 5, Step E using Intermediate iv-2 and tributyl(imidazo[1,5-a]pyridine-8-yl)stannane		Method 3: 2.85 min, m/z 428.4 [M+H] ⁺

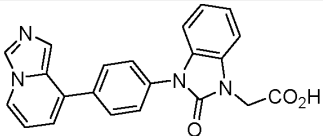
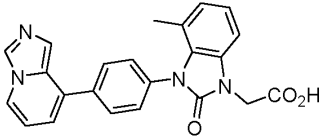
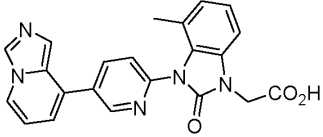
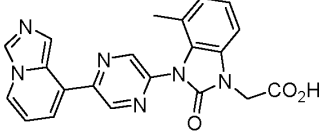
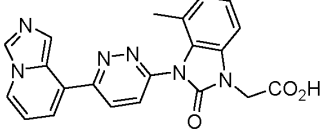
Intermediates **ix-5** and **ix-6** were synthesised according to the following procedure.

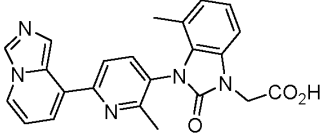
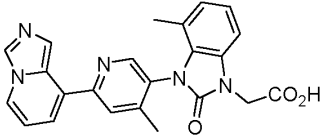
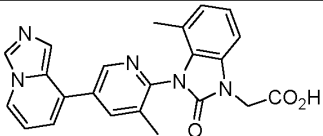
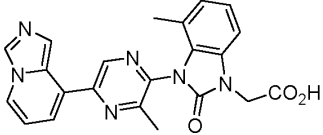
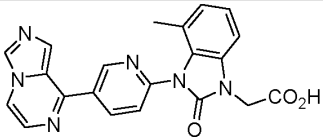
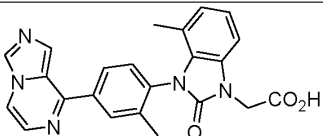
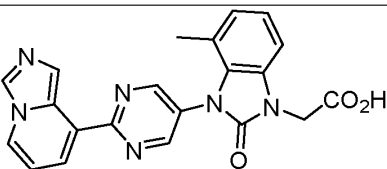
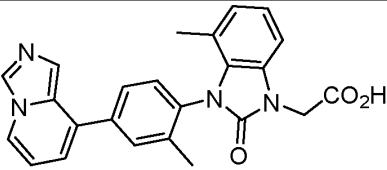
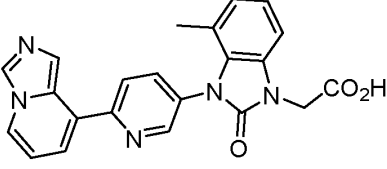
Intermediate **ix-5**: A mixture of CuI (32 mg, 0.15 mmol), Intermediate **iv-9** (120 mg, 0.31 mmol), LiCl (39 mg, 0.92 mmol), Pd(PPh₃)₄ (35 mg, 0.005 mmol) and tributyl(imidazo[1,5-a]pyridin-8-yl)stannane (150 mg, 0.37 mmol) in toluene (3 mL) was stirred at 120 °C under N₂ atmosphere overnight. The mixture was allowed to return to room temperature, quenched with water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over Na₂CO₃ and concentrated in vacuo. Further purification by P-TLC (Pet.ether/EtOAc 1:2) afforded ethyl 2-[3-(5-imidazo[1,5-a]pyridin-8-yl)pyrazin-2-yl]-4-methyl-2-oxo-benzimidazol-1-yl]acetate (40 mg, 0.09 mmol, 30% yield).

Intermediate **ix-6**: A mixture of CuI (80.5 mg, 0.38 mmol), Intermediate **iv-7** (300 mg, 0.77 mmol), LiCl (97.5 mg, 2.30 mmol), Pd(PPh₃)₄ (88.6 mg, 0.08 mmol) and tributyl(imidazo[1,5-a]pyridin-8-yl)stannane (375 mg, 0.92 mmol) in toluene (0.5 mL) was stirred at 120 °C under N₂ atmosphere overnight. The reaction was filtered and purified p-HPLC to give ethyl 2-[3-(6-imidazo[1,5-a]pyridin-8-yl)pyridazin-3-yl]-4-methyl-2-oxo-benzimidazol-1-yl]acetate (60 mg, 0.14 mmol, 19% yield).

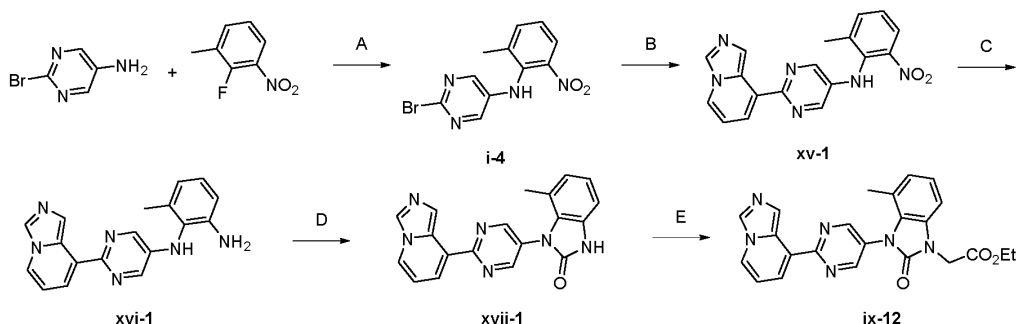
Intermediates synthesised following the same procedure as Intermediate **x-1** (Route 3) replacing ethyl 2-[3-(4-imidazo[1,5-a]pyridin-8-yl)phenyl]-4-methyl-2-oxo-benzimidazol-1-yl]acetate in Step G for the described building block are also described in Table 12.

Table 12.

Intermediate number	Intermediate structure	LC-MS
Intermediate x-1 Route 3, Step G:		Method 3: 2.68 min, m/z 385.1 [M+H] ⁺
Intermediate x-2 Route 3, Step G:		Method 3: 2.75 min, m/z 399.0 [M+H] ⁺
Intermediate x-3 Route 3, Step G:		Method 3: 2.65 min, m/z 400.2 [M+H] ⁺
Intermediate x-4 Route 3, Step G:		Method 3: 2.62 min, m/z 401.2 [M+H] ⁺
Intermediate x-5 Route 3, Step G:		Method 3: 2.55 min, m/z 401.2 [M+H] ⁺

Intermediate x-6 Route 5, Step F:		Method 4: 0.82 min, m/z, 414.2 [M+H] ⁺
Intermediate x-7 Route 5, Step F:		Method 3: 2.48 min, m/z, 414.3 [M+H] ⁺
Intermediate x-8 Route 3, Step G:		¹ H NMR (400 MHz, DMSO-d ₆): 8.80 (s, 1H), 8.54 (s, 1H), 8.47 – 8.42 (m, 1H), 8.29 (s, 1H), 7.59 (s, 1H), 7.16 – 7.00 (m, 3H), 6.89 – 6.79 (m, 2H), 4.74 – 4.60 (m, 2H), 2.29 (s, 3H), 1.74 (s, 3H).
Intermediate x-9 Route 5, Step F:		Method 3: 2.45 min, m/z, 415.3 [M+H] ⁺
Intermediate x-10 Route 3, Step G:		Method 3: 2.62 min, m/z 401.2 [M+H] ⁺
Intermediate x-11 Route 3, Step G:		Method 3: 2.84 min, m/z 414.2 [M+H] ⁺
Intermediate x-12 Route 3, Step G		Method 3: 0.93 min, m/z 401.2 [M+H] ⁺
Intermediate x-13 Route 3, Step G		Method 3: 2.68 min, m/z 413.3 [M+H] ⁺
Intermediate x-14 Route 3, Step G		Method 3: 1.25 min, m/z 400.3 [M+H] ⁺

Route 7



Step A: Synthesis of **i-4**: NaH (462 mg, 11.56 mmol, 2.0 eq) was added slowly to a solution of 2-fluoro-1-methyl-3-nitrobenzene (896 mg, 6.45 mmol, 1 eq) in DMF (15 mL) at 0 °C under N₂, and stirred for 0.5 h. 2-bromopyrimidin-5-amine (1.00 g, 5.78 mmol, 1 eq) in DMF (10 mL) was added slowly and stirred for 16 h. The mixture was diluted with water (5 mL) and extracted with EA (200 mL x 3). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄ and concentrated in vacuum and purified by silica gel column eluting with Pet.ether/EtOAc (10:1 to 1:1, v/v) to give 2-bromo-N-(2-methyl-6-nitro-phenyl)pyrimidin-5-amine (1.30 g, 73%).

UPLCMS (ES⁺, Method 3): 1.34 min, m/z 308.6 / 310.6 [M]⁺ / [M+2]⁺

Step B: Synthesis of **xiv-1**: A mixture of 2-bromo-N-(2-methyl-6-nitrophenyl)pyrimidin-5-amine (424 mg, 1.37 mmol, 1.0 eq), 8-(tributylstannyl)imidazo[1,5-a]pyridine (670 mg, 1.64 mmol, 1.2 eq), Pd(PPh₃)₄ (158 mg, 0.14 mmol, 0.1 eq), CuI (78 mg, 0.41 mmol, 0.3 eq) and LiCl (174 mg, 4.11 mmol, 3.0 eq) in toluene (10 mL) was stirred at 120 °C under N₂ overnight. The mixture was concentrated and the crude was diluted with water (80 mL), then extracted with ethyl acetate (20 mL x 3). The organic solution was washed with brine (30 mL), dried over Na₂SO₄ and concentrated in vacuum. The crude was purified by silica gel column eluting with DCM/MeOH (200:1 to 150:1, v/v) to give 2-imidazo[1,5-a]pyridin-8-yl-N-(2-methyl-6-nitro-phenyl)pyrimidin-5-amine (310 mg, 65%) as a yellow solid.

UPLCMS (ES⁺ Method 3): 1.07 min, m/z 347.1 [M+H]⁺

Step C: Synthesis of **xv-1**: A mixture of 2-(imidazo[1,5-a]pyridin-8-yl)-N-(2-methyl-6-nitrophenyl)pyrimidin-5-amine (115 mg, 0.33 mmol, 1.0 eq), Fe (93 mg, 1.66 mmol, 5.0 eq) and NH₄Cl (90 mg, 1.66 mmol, 5.0 eq) in EtOH/H₂O (2:1, 9 mL) was stirred at 80 °C under N₂ for 2 hours. The mixture was filtered through a Buchner funnel, and the solid washed with Ethanol (20 mL). The filtrate was concentrated and diluted with water (40 mL), then extracted with EtOAc (10 mL x 3). The combined organics were washed with brine (15 mL), dried over Na₂SO₄ and concentrated in vacuo to give N2-(2-imidazo[1,5-a]pyridin-8-ylpyrimidin-5-yl)-3-methyl-benzene-1,2-diamine (110 mg, assumed quantitative) as a yellow solid. **UPLCMS** (ES⁺, Method 3): 1.00 min, m/z 317.1 [M+H]⁺

Step D: Synthesis of **xvi-1**: A mixture of N1-(2-(imidazo[1,5-a]pyridin-8-yl)pyrimidin-5-yl)-6-methylbenzene-1,2-diamine (190 mg, 0.60 mmol, 1.0 eq) and CDI (292 mg, 1.80 mmol, 3.0 eq) in DMF (1.5 mL) was stirred at 100 °C under N₂ and overnight. The reaction mixture was diluted with water (30 mL) and was extracted with EtOAc (8 mL x 5). The combined organics were washed with brine (20 mL x 3), dried over Na₂SO₄ and concentrated in vacuum. The crude was purified by silica gel column eluting

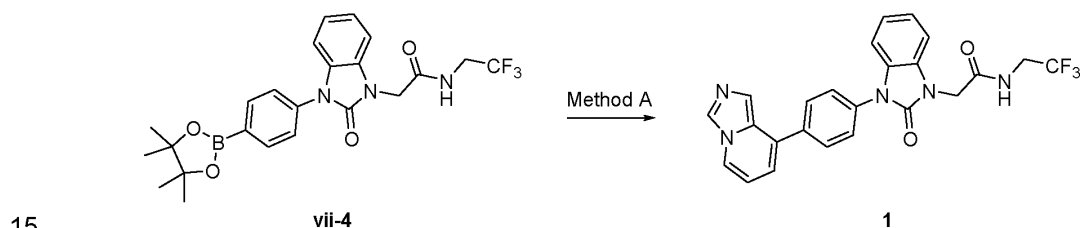
with Pet. ether/EtOAc (100:1 to 80:1, v/v) to give 3-(2-imidazo[1,5-a]pyridin-8-yl)pyrimidin-5-yl)-4-methyl-1H-benzimidazol-2-one (6 mg, 29%) as a yellow solid.

UPLCMS (ES⁺ Method 3): 0.97 min, m/z 343.1 [M+H]⁺

Step E: Synthesis of **ix-12**: A mixture of 1-(2-(imidazo[1,5-a]pyridin-8-yl)pyrimidin-5-yl)-7-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (155 mg, 0.45 mmol, 1.0 eq), ethyl 2-bromoacetate (113 mg, 0.68 mmol, 1.5 eq) and Cs₂CO₃ (295 mg, 0.91 mmol, 2.0 eq) in MeCN (3 mL) was stirred at room temperature under N₂ for 2 hours. The mixture was concentrated in vacuum. The residue was diluted with water (20 mL) and extracted with EtOAc (5 mL x 4). The combined organics were washed with brine (10 mL), dried over Na₂SO₄ and concentrated in vacuum. The crude was purified by silica gel column eluting with DCM/MeOH (100:1 to 80:1, v/v) to give ethyl 2-[3-(2-imidazo[1,5-a]pyridin-8-yl)pyrimidin-5-yl)-4-methyl-2-oxo-benzimidazol-1-yl]acetate (155 mg, 80%) as a yellow solid.

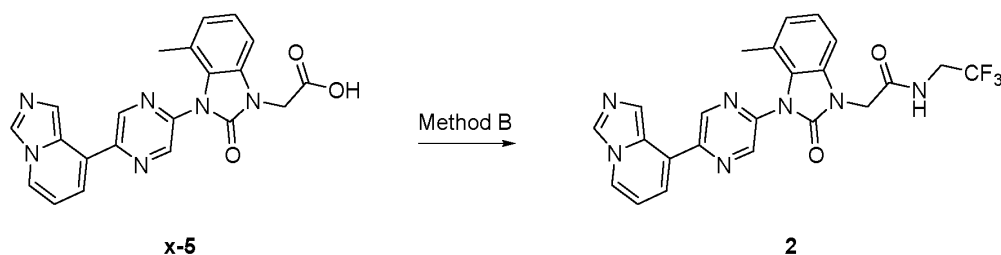
UPLCMS (ES⁺ Method 3): 1.20 min, m/z 429.1 [M+H]⁺

Synthesis of Final Compounds



Method A: Synthesis of example 1: To a solution of potassium carbonate (65 mg, 0.47 mmol), 2-[2-oxo-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]benzimidazol-1-yl]-N-(2,2,2-trifluoroethyl)acetamide (74 mg, 0.16 mmol) and 8-bromo-imidazo[1,5-a]pyridine (34 mg, 0.17 mmol) in degassed 1,4-Dioxane (4.5 mL) and water (0.5 mL) under nitrogen was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium II (11 mg, 0.020 mmol) and the flask evacuated and refilled with nitrogen. The reaction was heated at 90 °C for 16 h. The reaction was concentrated to dryness and the crude was purified by flash column chromatography eluting 100% EtOAc to 10% MeOH in DCM and EtOAc. The desired fractions were concentrated to dryness in vacuo to provide 2-[3-(4-imidazo[1,5-a]pyridin-8-ylphenyl)-2-oxo-benzimidazol-1-yl]-N-(2,2,2-trifluoroethyl)acetamide (11 mg, 0.02 mmol, 15% yield) as a yellow solid. **UPLCMS** (ES⁺, Method 1): 2.88 min, m/z 466.8 [M+H]⁺

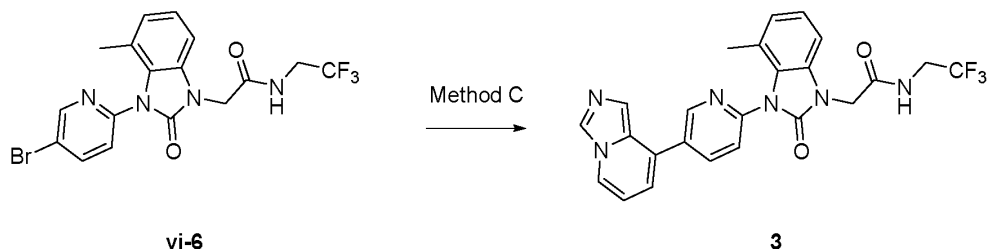
25 **¹H NMR (400 MHz, DMSO-d₆)** δ 9.08 – 8.96 (m, 1H), 8.55 (d, J = 0.7 Hz, 1H), 8.49 – 8.41 (m, 1H), 8.02 – 7.95 (m, 2H), 7.81 – 7.72 (m, 2H), 7.59 (s, 1H), 7.29 – 7.12 (m, 4H), 7.06 – 6.99 (m, 1H), 6.90 – 6.79 (m, 1H), 4.73 (s, 2H), 4.10 – 3.96 (m, 2H) ppm.



Method B: Synthesis of example 2: A mixture of 2-[3-(5-imidazo[1,5-a]pyridin-8-ylpyrazin-2-yl)-4-methyl-2-oxo-benzimidazol-1-yl]acetic acid (30 mg, 0.0749 mmol, 1.0 eq), trifluoroethylamine (11 mg, 0.112 mmol, 1.5 eq), HATU (34 mg, 0.0899 mmol, 1.2 eq) and DIPEA (29 mg, 0.225 mmol, 3.0 eq) in DMF (2 mL) was stirred at 25 °C for 4 h. The reaction mixture was diluted with water (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (10 mL x 3) and dried over Na₂SO₄. The combined organic layers were concentrated under vacuum and purified by P-TLC (DCM/MeOH 15:1) to provide 2-[3-(5-imidazo[1,5-a]pyridin-8-ylpyrazin-2-yl)-4-methyl-2-oxo-benzimidazol-1-yl]-N-(2,2,2-trifluoroethyl)acetamide (11 mg, 31%) as a yellow solid.

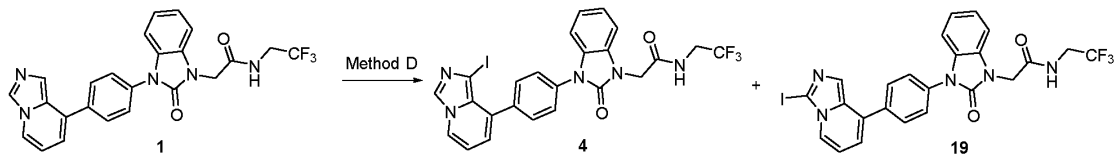
UPLCMS (ES⁺, Method 3): 2.88 min, m/z 482.2 [M+H]⁺

¹H NMR (400 MHz, DMSO-d₆) δ 9.47 (s, 1H), 9.14 (s, 1H), 9.08 – 9.02 (m, 1H), 8.64 – 8.58 (m, 2H), 8.11 (s, 1H), 7.80 (d, J = 6.8 Hz, 1H), 7.18 – 7.12 (m, 1H), 7.08 (d, J = 8.6 Hz, 1H), 7.00 – 6.91 (m, 2H), 4.72 (s, 2H), 4.07 – 3.94 (m, 2H), 2.08 – 1.95 (m, 3H) ppm.



Method C: Synthesis of example 3: A solution of 2-[3-(5-bromo-2-pyridyl)-4-methyl-2-oxo-benzimidazol-1-yl]-N-(2,2,2-trifluoroethyl)acetamide (100 mg, 0.23 mmol, 1.0 eq), tributyl(imidazo[1,5-a]pyridin-8-yl)stannane (110 mg, 0.27 mmol, 1.2 eq), Pd(PPh₃)₄ (26.1 mg, 0.023 mmol, 0.1 eq), LiCl (29 mg, 0.68 mmol, 3.0 eq), and CuI (24 mg, 0.11 mmol, 0.5 eq) in toluene (0.5 mL) was stirred at 120 °C under N₂ overnight. The mixture was diluted with EtOAc (3 mL) and washed with H₂O (5 mL x 3). The organic layers were washed with EtOAc (5 mL x 3), combined, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The reaction mixture was purified by Prep-HPLC to provide 2-[3-(5-imidazo[1,5-a]pyridin-8-ylpyrazin-2-yl)-4-methyl-2-oxo-benzimidazol-1-yl]-N-(2,2,2-trifluoroethyl)acetamide (3.3 mg, 0.01 mmol, 3% yield) as a yellow solid. **UPLCMS** (ES⁺, Method 3): 2.88 min, m/z 481.3 [M+H]⁺

¹H NMR (400 MHz, DMSO-d₆) δ 9.00 – 8.97 (m, 3H), 8.50 (d, J = 6.9 Hz, 1H), 8.45–8.39 (m, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.24 (d, J = 6.7 Hz, 1H), 7.11 – 7.03 (m, 1H), 7.03 – 6.95 (m, 2H), 6.90 (d, J = 7.4 Hz, 1H), 4.66 (s, 2H), 4.03 – 3.92 (m, 2H), 1.92 (s, 3H) ppm

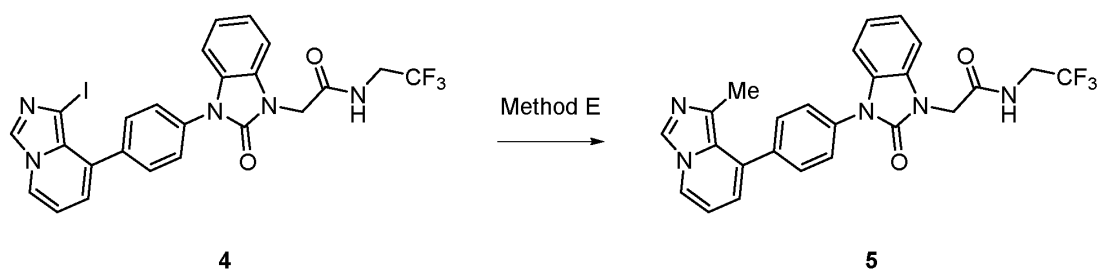


Method D: Synthesis of example 4 and 19: To a solution of 2-[3-(4-imidazo[1,5-a]pyridin-8-ylphenyl)-2-oxo-benzimidazol-1-yl]-N-(2,2,2-trifluoroethyl)acetamide (577 mg, 1.24 mmol, 1.0 eq) in THF (5 mL) was added N-iodosuccinimide (225 mg, 1.00 mmol, 1.0 eq). The reaction mixture was concentrated in vacuum and purified by SGC eluting Pet.Ether/EtOAc (1:1) then prep-HPLC to afford 2-[3-(4-(1-iodoimidazo[1,5-a]pyridin-8-yl)phenyl)-2-oxo-benzimidazol-1-yl]-N-(2,2,2-trifluoroethyl)acetamide (70

mg, 0.12 mmol, 10% yield) as a yellow solid and 2-[3-[4-(3-iodoimidazo[1,5-a]pyridin-8-yl)phenyl]-2-oxo-benzimidazol-1-yl]-N-(2,2,2-trifluoroethyl)acetamide (40 mg, 0.07 mmol, 5% yield) as a yellow solid. 2-[3-[4-(1-iodoimidazo[1,5-a]pyridin-8-yl)phenyl]-2-oxo-benzimidazol-1-yl]-N-(2,2,2-trifluoroethyl)acetamide (**4**). **UPLCMS** (ES⁺, Method 3): 1.45 min, m/z 591.8 [M+H]⁺

- 5 **¹H NMR (400 MHz, DMSO-d₆)** δ 9.07 – 8.99 (m, 1H), 8.62 (s, 1H), 8.51 (d, J = 6.8 Hz, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.25 – 7.10 (m, 4H), 6.90 – 6.80 (m, 2H), 4.73 (s, 2H), 4.09 – 3.96 (m, 2H) ppm. 2-[3-[4-(3-iodoimidazo[1,5-a]pyridin-8-yl)phenyl]-2-oxo-benzimidazol-1-yl]-N-(2,2,2-trifluoroethyl)acetamide (**19**). **UPLCMS** (ES⁺, Method 3): 1.58 min, m/z 591.8 [M+H]⁺

- 10 **¹H NMR (400 MHz, DMSO-d₆)** δ 9.06 – 8.99 (m, 1H), 8.16 (d, J = 7.1 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.80 – 7.71 (m, 3H), 7.26 (d, J = 7.6 Hz, 1H), 7.24 – 7.14 (m, 1H), 7.12 (d, J = 6.5 Hz, 1H), 7.05 – 6.99 (m, 1H), 4.73 (s, 2H), 4.09 – 3.96 (m, 2H), 2.11 (s, 2H) ppm.

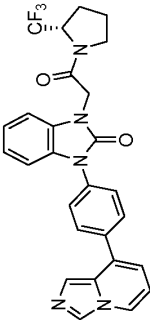
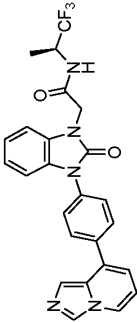
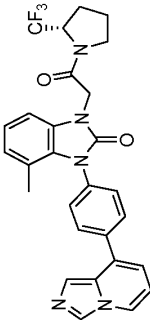
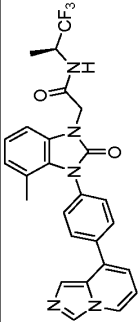
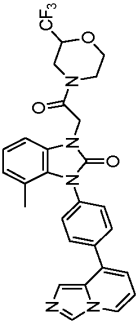
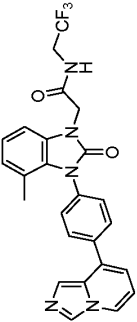


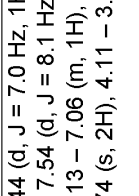
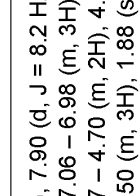
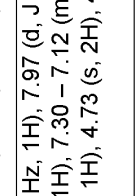
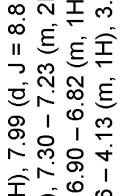
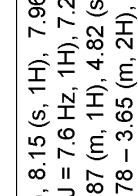
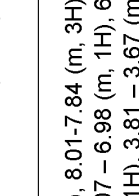
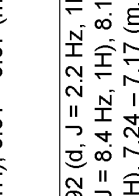
- Method E:** Synthesis of example **5**: To a solution of 2-[3-[4-(1-iodoimidazo[1,5-a]pyridin-8-yl)phenyl]-2-oxo-benzimidazol-1-yl]-N-(2,2,2-trifluoroethyl)acetamide (40 mg, 0.070 mmol) and methylboronic acid (12 mg, 0.20 mmol) potassium phosphate tribasic (43 mg, 0.20 mmol) in 1,4-dioxane (2 mL) and water (0.4 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (9.8 mg, 0.010 mmol). The resulting mixture was heated at 100 °C for 16 h. The crude material was purified via prep-HPLC to provide 2-[3-[4-(1-methylimidazo[1,5-a]pyridin-8-yl)phenyl]-2-oxo-benzimidazol-1-yl]-N-(2,2,2-trifluoroethyl)acetamide (2.7 mg, 8.3%).

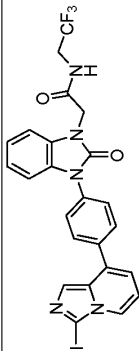
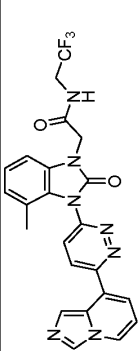
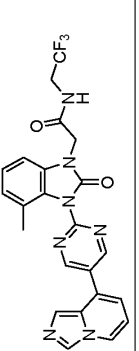
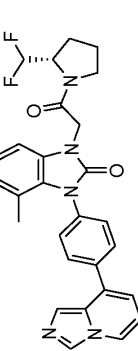
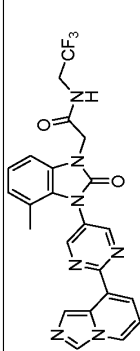
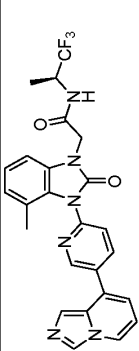
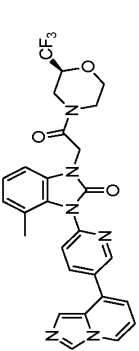
- 20 **UPLCMS** (ES⁺, Method 3): 2.75 min, m/z 480.3 [M+H]⁺

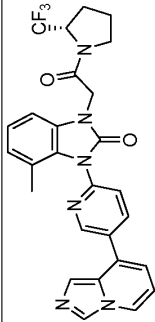
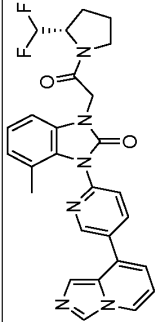
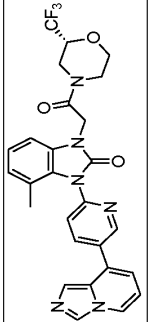
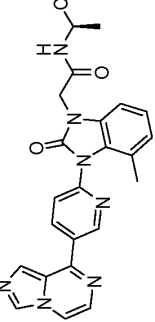
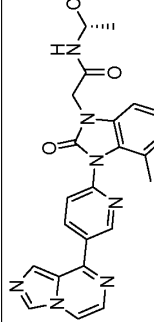
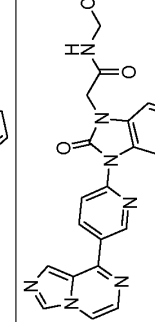
¹H NMR (400 MHz, DMSO-d₆) δ 9.08 – 9.00 (m, 1H), 8.42 (s, 1H), 8.32 (d, J = 7.0 Hz, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.29 – 7.11 (m, 4H), 6.77 – 6.66 (m, 1H), 6.63 (d, J = 6.5 Hz, 1H), 4.72 (s, 2H), 4.08 – 3.94 (m, 2H), 2.08 (s, 3H) ppm.

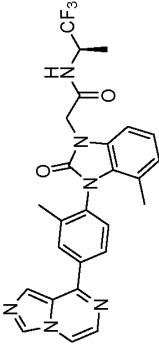
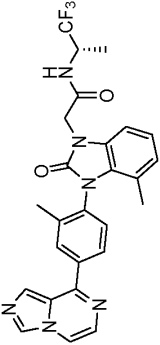
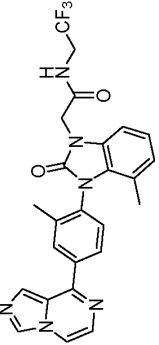
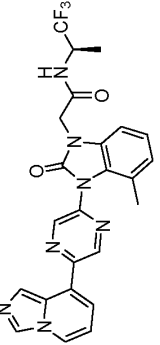
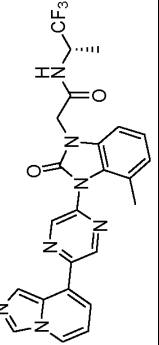
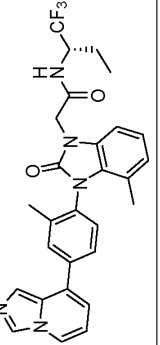
Table 13.

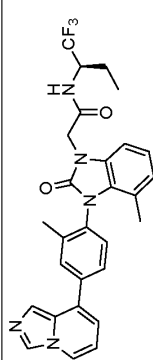
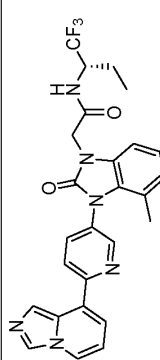
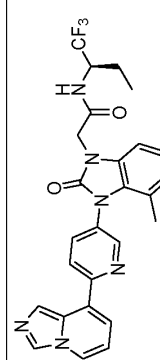
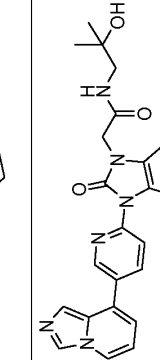
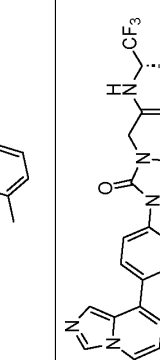
Example Number / Method	Structure	UPLC-MS (ES ⁺)	¹ H NMR (400 MHz, DMSO-d6)
Example 6 Method A		Method 3: 3.17 min, m/z 506.3 [M+H] ⁺	δ 8.56 (s, 1H), 8.44 (d, J = 7.0 Hz, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.6 Hz, 2H), 7.60 (s, 1H), 7.28 – 7.11 (m, 4H), 7.02 (d, J = 6.6 Hz, 1H), 6.88 – 6.82 (m, 1H), 5.32 – 4.66 (m, 3H), 3.98 – 3.76 (m, 2H), 2.24 – 1.92 (m, 4H) ppm.
Example 7 Method A		Method 3: 1.30 min, m/z 480.1 [M+H] ⁺	δ 8.97 (d, J = 8.8 Hz, 1H), 8.55 (s, 1H), 8.44 (d, J = 7.0 Hz, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.59 (s, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.22 – 7.11 (m, 3H), 7.02 (d, J = 6.7 Hz, 1H), 6.88 – 6.81 (m, 1H), 4.77 – 4.58 (m, 3H), 1.34 (d, J = 7.1 Hz, 3H) ppm.
Example 8 Method A		Method 3: 1.49 min, m/z 520.2 [M+H] ⁺	δ 8.51 (s, 1H), 8.41 (d, J = 4.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.53 (s, 1H), 7.03 – 7.00 (m, 3H), 6.85-6.75 (m, 2H), 4.86 – 4.68 (m, 3H), 3.83 – 3.64 (m, 2H), 2.15 – 2.01 (m, 4H), 1.89 (s, 3H) ppm.
Example 9 Method A		Method 4: 3.08 min, m/z 494.2 [M+H] ⁺	δ 8.93 (d, J = 8.8 Hz, 1H), 8.56 (s, 1H), 8.45 (d, J = 7.1 Hz, 1H), 7.94 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.3 Hz, 2H), 7.57 (s, 1H), 7.12 – 6.99 (m, 3H), 6.94 – 6.81 (m, 2H), 4.76 – 4.54 (m, 3H), 1.93 (s, 3H), 1.33 (d, J = 7.1 Hz, 3H) ppm.
Example 10 Method A		Method 3: 3.15 min, m/z 536.3 [M+H] ⁺	δ 8.51 (s, 1H), 8.41 (d, J = 7.0 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.3 Hz, 2H), 7.53 (s, 1H), 7.09 – 6.99 (m, 3H), 6.86 – 6.79 (m, 2H), 5.11 – 4.97 (m, 1H), 4.90 – 4.78 (m, 1H), 4.45 – 3.95 (m, 4H), 3.81 – 3.53 (m, 1H), 3.47 – 3.36 (m, 1H), 2.98 – 2.85 (m, 1H), 1.89 (s, 3H) ppm.
Example 11 Method A		Method 3: 2.98 min, m/z 480.2 [M+H] ⁺	δ 8.97-8.91 (m, 1H), 8.51 (s, 1H), 8.41 (d, J = 7.1 Hz, 1H), 7.91 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.2 Hz, 2H), 7.52 (s, 1H), 7.06 – 6.97 (m, 3H), 6.89 – 6.77 (m, 2H), 4.64 (s, 2H), 4.02 – 3.93 (m, 2H), 1.89 (s, 3H) ppm.

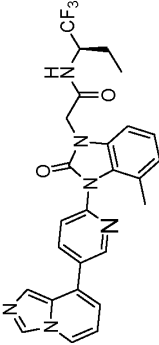
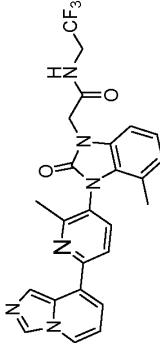
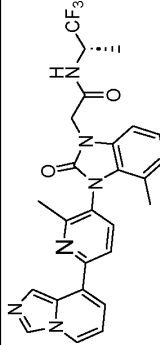
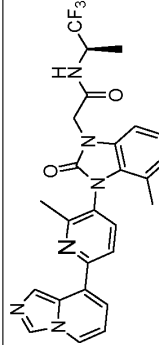
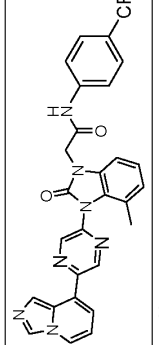
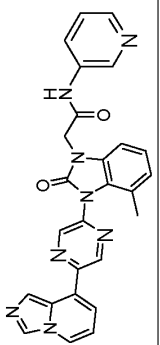
Example 12 Method A:		Method 3: 3.05 min, m/z 480.3 [M+H] ⁺	δ 9.09 – 8.99 (m, 1H), 8.55 (s, 1H), 8.44 (d, J = 7.0 Hz, 1H), 7.87 (s, 1H), 7.84 – 7.76 (m, 1H), 7.61 (s, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.19 – 7.14 (m, 1H), 7.13 – 7.06 (m, 1H), 7.03 (d, J = 6.6 Hz, 1H), 6.90 – 6.75 (m, 2H), 4.74 (s, 2H), 4.11 – 3.96 (m, 2H), 2.22 (s, 3H) ppm.
Example 13 Method B		Method 3: 3.08 min, m/z 536.0 [M+H] ⁺	δ 8.51 (s, 1H), 8.39 (d, J = 7.0 Hz, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.52 (s, 1H), 7.06 – 6.98 (m, 3H), 6.88 – 6.80 (m, 2H), 5.16 – 5.09 (m, 1H), 4.97 – 4.70 (m, 2H), 4.19 – 4.11 (m, 1H), 3.95 – 3.86 (m, 2H), 3.70 – 3.50 (m, 3H), 1.88 (s, 3H) ppm.
Example 14 Method A		Method 3: 2.75 min, m/z 480.2 [M+H] ⁺	δ 9.90 – 8.98 (m, 1H), 8.17 (d, J = 7.1 Hz, 1H), 7.97 (d, J = 8.6 Hz, 2H), 7.75 (d, J = 8.6 Hz, 2H), 7.49 (s, 1H), 7.30 – 7.12 (m, 4H), 6.98 (d, J = 7.9 Hz, 1H), 6.85 (t, J = 6.8 Hz, 1H), 4.73 (s, 2H), 4.09 – 3.95 (m, 2H), 2.69 (s, 3H) ppm.
Example 15 Method B		Method 3: 2.92 min, m/z 470.2 [M+H] ⁺	δ 8.61 (brs, 1H), 8.44 (d, J = 6.8 Hz, 1H), 7.99 (d, J = 8.8 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H), 7.63 (brs, 1H), 7.30 – 7.23 (m, 2H), 7.23 – 7.10 (m, 2H), 7.83 (d, J = 6.6 Hz, 1H), 6.90 – 6.82 (m, 1H), 5.06 – 4.78 (m, 2H), 4.60 – 4.38 (m, 2H), 4.26 – 4.13 (m, 1H), 3.80 – 3.28 (m, 2H), 2.18 – 1.85 (m, 4H) ppm.
Example 16 Method B:		Method 3: 2.98 min, m/z 484.3 [M+H] ⁺	δ 9.44 (s, 1H), 8.60 (d, J = 7.1 Hz, 1H), 8.15 (s, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.69 – 7.62 (m, 2H), 7.38 (d, J = 7.6 Hz, 1H), 7.25 – 7.18 (m, 1H), 7.11 – 6.99 (m, 2H), 6.92 – 6.87 (m, 1H), 4.82 (s, 2H), 4.59 – 4.40 (m, 2H), 4.28 – 4.11 (m, 1H), 3.78 – 3.65 (m, 2H), 2.11 – 1.82 (m, 7H) ppm.
Example 17 Method B		Method 3: 3.05 min, m/z 488.2 [M+H] ⁺	δ 9.04 (s, 1H), 8.50 (d, J = 7.0 Hz, 1H), 8.01–7.84 (m, 3H), 7.74 (d, J = 8.3 Hz, 2H), 7.27 – 7.07 (m, 5H), 7.07 – 6.98 (m, 1H), 6.35 – 6.03 (m, 1H), 4.88 (s, 2H), 4.35 – 4.18 (m, 1H), 3.81 – 3.67 (m, 2H), 2.17 – 1.85 (m, 4H) ppm.
Example 18 Method C		Method 3: 1.07 min, m/z 481.1 [M+H] ⁺	δ 9.32 (s, 1H), 9.06 – 8.98 (m, 1H), 8.92 (d, J = 2.2 Hz, 1H), 8.67 (d, J = 7.1 Hz, 1H), 8.49 (s, 1H), 8.37 (d, J = 8.4 Hz, 1H), 8.16 (dd, J = 8.4, 2.5 Hz, 1H), 7.91 (d, J = 6.8 Hz, 1H), 7.24 – 7.17 (m, 1H), 7.15 – 7.03 (m, 2H), 6.97 – 6.91 (m, 1H), 4.71 (s, 2H), 4.14 – 3.94 (m, 2H), 1.96 (s, 3H) ppm.

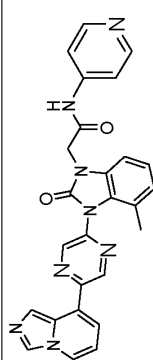
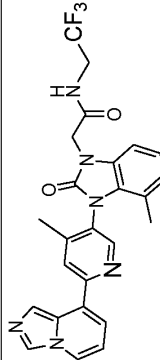
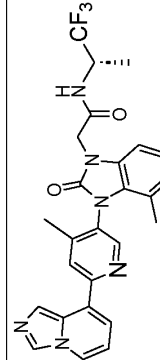
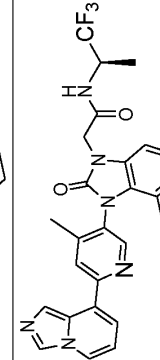
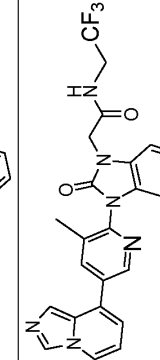
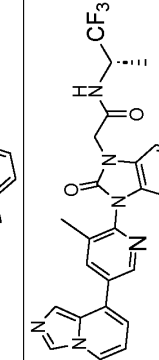
Example 19 Method D		Method 3: 1.58 min, m/z 591.8 [M+H] ⁺	δ 9.06 – 8.99 (m, 1H), 8.16 (d, J = 7.1 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.80 – 7.71 (m, 3H), 7.26 (d, J = 7.6 Hz, 1H), 7.24 – 7.10 (m, 4H), 7.05 – 6.99 (m, 1H), 4.73 (s, 2H), 4.09 – 3.96 (m, 2H) ppm.
Example 20 Method B		Method 3: 2.72 min, m/z 482.2 [M+H] ⁺	δ 9.24 (s, 1H), 9.11 – 9.01 (m, 1H), 8.77 – 8.72 (d, J = 8.8 Hz, 2H), 8.42 (s, 1H), 8.24 (d, J = 9.2 Hz, 1H), 7.96 (d, J = 7.4 Hz, 1H), 7.30 – 7.10 (m, 3H), 7.00 (d, J = 7.3 Hz, 1H), 4.74 (s, 2H), 4.08 – 3.96 (m, 2H), 1.98 (s, 3H) ppm.
Example 21 Method C		Method 4: 1.16 min, m/z 482.0 [M+H] ⁺	δ 9.45 (s, 2H), 9.10 – 9.03 (m, 1H), 8.61 (s, 1H), 8.53 (d, J = 7.1 Hz, 1H), 7.69 (s, 1H), 7.27 (d, J = 6.6 Hz, 1H), 7.16 – 7.09 (m, 1H), 7.06 (d, J = 7.6 Hz, 1H), 6.95 (d, J = 7.7 Hz, 1H), 6.92 – 6.87 (m, 1H), 4.71 (s, 2H), 4.10 – 3.93 (m, 2H), 1.90 (s, 3H) ppm.
Example 22 Method B		Method 3: 3.15 min, m/z 502.3 [M+H] ⁺	δ 9.22 (s, 1H), 8.53 (d, J = 7.0 Hz, 1H), 7.99 (s, 1H), 7.92 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 6.8 Hz, 1H), 7.11 – 7.01 (m, 3H), 6.85 (d, J = 7.2 Hz, 1H), 6.42 – 5.04 (m, 1H), 5.01 – 4.73 (m, 2H), 4.30 – 4.23 (d, 1H), 3.73 – 3.70 (m, 2H), 2.07 – 1.95 (m, 4H), 1.89 (s, 3H) ppm.
Example 23 Method B		Method 3: 1.13 min, m/z 482.2 [M+H] ⁺	δ 9.21 (s, 2H), 9.07 – 8.96 (m, 1H), 8.65 (d, J = 7.0 Hz, 1H), 8.58 (s, 1H), 8.30 (s, 1H), 8.17 (d, J = 7.6 Hz, 1H), 7.18 – 7.07 (m, 2H), 7.00 – 6.91 (m, 2H), 4.72 (s, 2H), 4.10 – 3.94 (m, 2H), 2.04 (s, 3H) ppm.
Example 24 Method B		Method 3: 3.02 min, m/z 495.3 [M+H] ⁺	δ 8.98 (d, J = 2.5 Hz, 1H), 8.93 (d, J = 7.3 Hz, 1H), 8.54 (s, 1H), 8.45 (d, J = 7.0 Hz, 1H), 8.42 (dd, J = 8.2, 2.5 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.56 (s, 1H), 7.16 – 6.98 (m, 3H), 6.95 – 6.83 (m, 2H), 4.70 – 4.55 (m, 3H), 1.91 (s, 3H), 1.30 (d, J = 7.0 Hz, 3H) ppm.
Example 25 Method B		Method 3: 3.08 min, m/z 537.4 [M+H] ⁺	δ 8.99 (s, 1H), 8.54 (s, 1H), 8.51 – 8.37 (m, 2H), 7.76 (d, J = 7.8 Hz, 1H), 7.56 (s, 1H), 7.16 – 7.00 (m, 3H), 6.94 – 6.78 (m, 2H), 5.14 – 4.94 (m, 1H), 4.94 – 4.79 (m, 1H), 4.50 – 3.93 (m, 4H), 3.83 – 3.31 (m, 2H) 3.00 – 2.83 (m, 1H), 1.91 (s, 3H) ppm.

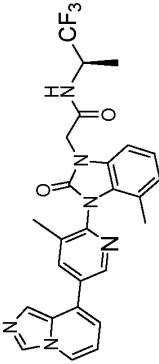
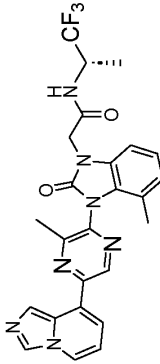
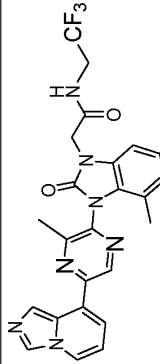
Example 26 Method B		Method 3: 3.15 min, m/z 521.3 [M+H] ⁺	δ 9.03 (d, J = 2.2 Hz, 1H), 8.59 (s, 1H), 8.52 – 8.49 (d, 1H), 8.46 (dd, J = 8.1, 2.5 Hz, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.60 (s, 1H), 7.15 (d, J = 7.1 Hz, 1H), 7.12 – 7.05 (m, 2H), 6.95 – 6.91 (m, 1H), 6.91 – 6.84 (m, 1H), 5.32 – 4.69 (m, 3H), 3.96 – 3.66 (m, 2H), 2.24 – 2.02 (m, 4H), 1.96 (s, 3H) ppm.
Example 27 Method B		Method 3: 3.02 min, m/z 503.3 [M+H] ⁺	δ 8.99 (d, J = 2.4 Hz, 1H), 8.55 (s, 1H), 8.50 – 8.39 (m, 2H), 7.77 (d, J = 8.2 Hz, 1H), 7.57 (s, 1H), 7.11 (d, J = 6.6 Hz, 1H), 7.09 – 7.02 (m, 2H), 6.92-6.81 (m, 2H), 6.34 – 6.01 (m, 1H), 4.84 (s, 2H), 4.34 – 4.20 (m, 1H), 3.79 – 3.51 (m, 2H), 2.10 – 1.93 (m, 4H), 1.91 (s, 3H) ppm.
Example 28 Method B		Method 3: 3.12 min, m/z 537.3 [M+H] ⁺	δ 8.99 (s, 1H), 8.55 (s, 1H), 8.49-8.38 (m, 2H), 7.76 (d, J = 8.1 Hz, 1H), 7.57 (s, 1H), 7.15-7.00 (m, 3H), 6.94 – 6.78 (m, 2H), 5.16-4.95 (m, 1H), 4.94-4.78 (m, 1H), 4.48-3.93 (m, 4H), 3.82 – 3.32 (m, 2H), 3.00-2.83 (m, 1H), 1.91 (s, 3H) ppm.
Example 29 Method B		Method 3: 3.12 min, m/z 496.2 [M+H] ⁺	δ 9.32 (s, 1H), 8.96 (d, J = 8.8 Hz, 1H), 8.80 – 8.71 (m, 2H), 8.48 (d, J = 4.8 Hz, 1H), 8.19 (s, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 4.8 Hz, 1H), 7.17 – 7.09 (m, 1H), 7.04 (d, J = 8.1 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 4.74-4.59 (m, 3H), 1.97 (s, 3H), 1.33 (d, J = 7.5 Hz, 3H) ppm.
Example 30 Method B		Method 3: 3.12 min, m/z 496.3 [M+H] ⁺	δ 9.32 (d, J = 2.3 Hz, 1H), 8.98 (d, J = 8.8 Hz, 1H), 8.79 – 8.71 (m, 2H), 8.48 (d, J = 4.9 Hz, 1H), 8.19 (s, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 4.8 Hz, 1H), 7.16 – 7.09 (m, 1H), 7.04 (d, J = 7.8 Hz, 1H), 6.95 (d, J = 7.7 Hz, 1H), 4.73 – 4.58 (m, 3H), 1.98 (s, 3H), 1.33 (d, J = 7.1 Hz, 3H) ppm.
Example 31 Method B		Method 3: 3.02 min, m/z 482.2 [M+H] ⁺	δ 9.28 (s, 1H), 9.02-8.95 (m, 1H), 8.77-8.67 (m, 2H), 8.44 (d, J = 4.7 Hz, 1H), 8.15 (s, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 4.8 Hz, 1H), 7.12-7.04 (m, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.91 (d, J = 7.5 Hz, 1H), 4.66 (s, 2H), 4.04-3.91 (m, 2H), 1.93 (s, 3H).

Example 32 Method B		Method 3: 3.15 min, m/z 509.2 [M+H] ⁺	δ 8.94 – 8.85 (m, 1H), 8.69 (s, 1H), 8.42 – 8.37 (m, 1H), 8.13 – 8.08 (m, 2H), 8.08 – 8.03 (m, 1H), 7.73 (d, J = 4.8 Hz, 1H), 7.59 – 7.52 (m, 1H), 7.0611 – 6.96 (m, 2H), 6.86 – 6.81 (m, 1H), 4.70 – 4.54 (m, 3H), 2.18 (s, 3H), 1.78 (s, 3H), 1.29 (d, J = 7.0 Hz, 3H) ppm.
Example 33 Method B		Method 3: 3.30 min, m/z 509.2 [M+H] ⁺	δ 8.95 – 8.86 (m, 1H), 8.69 (s, 1H), 8.39 (d, J = 4.8 Hz, 1H), 8.13 – 8.08 (m, 2H), 8.08 – 8.03 (m, 1H), 7.73 (d, J = 4.8 Hz, 1H), 7.59 – 7.52 (m, 1H), 7.06 – 6.96 (m, 2H), 6.86 – 6.80 (m, 1H), 4.71 – 4.56 (m, 3H), 2.18 (s, 3H), 1.78 (s, 3H), 1.30 (d, J = 6.9 Hz, 3H) ppm.
Example 34 Method B		Method 3: 3.18 min, m/z 495.2 [M+H] ⁺	δ 9.00 – 8.92 (m, 1H), 8.69 (s, 1H), 8.39 (d, J = 4.8 Hz, 1H), 8.14 – 8.08 (m, 2H), 8.08 – 8.03 (m, 1H), 7.73 (d, J = 4.8 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.06 – 6.98 (m, 2H), 6.87 – 6.80 (m, 1H), 4.66 (s, 2H), 4.05 – 3.91 (m, 2H), 2.19 (s, 3H), 1.78 (s, 3H) ppm.
Example 35 Method B		Method 3: 2.95 min, m/z 496.1 [M+H] ⁺	δ 9.45 – 9.41 (m, 1H), 9.12 – 9.07 (m, 1H), 8.93 (d, J = 8.8 Hz, 1H), 8.59 – 8.52 (m, 2H), 8.07 (s, 1H), 7.76 (d, J = 6.8 Hz, 1H), 7.15 – 7.08 (m, 1H), 7.03 (d, J = 7.8 Hz, 1H), 6.94 (d, J = 7.7 Hz, 1H), 6.92 – 6.86 (m, 1H), 4.71 – 4.58 (m, 3H), 1.97 (s, 3H), 1.29 (d, J = 7.0 Hz, 3H) ppm.
Example 36 Method B		Method 3: 2.92 min, m/z, 496.2 [M+H] ⁺	δ 9.47 (s, 1H), 9.11 (s, 1H), 9.04 – 8.91 (m, 2H), 8.63 (d, J = 6.8 Hz, 1H), 8.30 (s, 1H), 7.92 (d, J = 6.8 Hz, 1H), 7.16 – 7.00 (m, 3H), 6.94 (d, J = 7.4 Hz, 1H), 4.71 – 4.55 (m, 3H), 1.97 (s, 3H), 1.33-1.20 (m, 3H) ppm.
Example 37 Method B:		Method 3: 3.23 min, m/z 522.4 [M+H] ⁺	δ 8.84 – 8.74 (m, 1H), 8.53 (s, 1H), 8.41 (d, J = 6.9 Hz, 1H), 7.78 (s, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.57 – 7.46 (m, 2H), 7.06 – 6.95 (m, 3H), 6.86 – 6.77 (m, 2H), 4.74 – 4.60 (m, 2H), 4.49 – 4.35 (m, 1H), 2.19 – 2.09 (m, 3H), 1.85 – 1.72 (m, 4H), 1.65 – 1.50 (m, 1H), 0.94 (t, J = 6.9 Hz, 3H) ppm

Example 38 Method B:		Method 3: 3.25 min, m/z 522.4 [M+H] ⁺	δ 8.89 – 8.74 (m, 1H), 8.53 (s, 1H), 8.47 – 8.36 (m, 1H), 7.78 (s, 1H), 7.75 – 7.67 (m, 1H), 7.60 – 7.45 (m, 2H), 7.08 – 6.93 (m, 3H), 6.89 – 6.75 (m, 2H), 4.77 – 4.60 (m, 2H), 4.51 – 4.33 (m, 1H), 2.14 (s, 3H), 1.86 – 1.70 (m, 4H), 1.65 – 1.50 (m, 1H), 1.00 – 0.88 (m, 3H) ppm
Example 39 Method B:		Method 3: 3.05 min, 509.4 [M+H] ⁺	δ 8.86 (d, J = 2.3 Hz, 1H), 8.79 (d, J = 9.2 Hz, 1H), 8.69 (s, 1H), 8.53 (d, J = 7.0 Hz, 1H), 8.26 (d, J = 8.5 Hz, 1H), 8.14 – 8.05 (m, 2H), 7.64 (d, J = 6.8 Hz, 1H), 7.09 – 6.99 (m, 2H), 6.95 – 6.86 (m, 2H), 4.74 – 4.62 (m, 2H), 4.49 – 4.36 (m, 1H), 1.92 (s, 3H), 1.84 – 1.71 (m, 1H), 1.64 – 1.50 (m, 1H), 0.94 (t, J = 7.3 Hz, 3H) ppm
Example 40 Method B:		Method 3: 3.02 min, m/z 509.4 [M+H] ⁺	δ 8.85 (d, J = 2.2 Hz, 1H), 8.79 (d, J = 9.2 Hz, 1H), 8.53 – 8.47 (m, 2H), 8.24 (d, J = 8.5 Hz, 1H), 8.06 (dd, J = 8.5, 2.6 Hz, 1H), 8.01 (s, 1H), 7.57 (d, J = 6.6 Hz, 1H), 7.10 – 6.98 (m, 2H), 6.91 – 6.82 (m, 2H), 4.75 – 4.61 (m, 2H), 4.48 – 4.36 (m, 1H), 1.92 (s, 3H), 1.83 – 1.72 (m, 1H), 1.64 – 1.50 (m, 1H), 0.94 (t, J = 7.3 Hz, 3H) ppm
Example 41 Method B:		Method 4: 0.79 min, m/z 471.2 [M+H] ⁺	δ 9.00 – 8.95 (m, 1H), 8.55 (s, 1H), 8.46 (d, J = 7.0 Hz, 1H), 8.44 – 8.38 (m, 1H), 8.23 – 8.16 (m, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.56 (s, 1H), 7.11 (d, J = 6.6 Hz, 1H), 7.09 – 6.97 (m, 2H), 6.92 – 6.81 (m, 2H), 4.61 (s, 2H), 4.51 (s, 1H), 3.09 (d, J = 6.0 Hz, 2H), 1.91 (s, 3H), 1.08 (s, 6H) ppm
Example 42 Method B		Method 4: 1.35 min, m/z, 509.2 [M+H] ⁺	δ 9.03 – 8.97 (m, 2H), 8.82 (d, J = 9.1 Hz, 1H), 8.53 (d, J = 7.0 Hz, 1H), 8.43 (dd, J = 8.3, 2.5 Hz, 1H), 7.89 (br s, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.27 (d, J = 6.6 Hz, 1H), 7.11 – 6.98 (m, 3H), 6.90 (d, J = 7.5 Hz, 1H), 4.74 – 4.62 (m, 2H), 4.45 – 4.39 (m, 1H), 1.92 (s, 3H), 1.84 – 1.72 (m, 1H), 1.64 – 1.50 (m, 1H), 0.94 (t, J = 7.3 Hz, 3H) ppm.

Example 43 Method B		Method 4: 1.36 min, m/z, 509.2 [M+H] ⁺	δ 9.02 – 8.94 (m, 2H), 8.82 (d, J = 9.2 Hz, 1H), 8.53 (d, J = 7.0 Hz, 1H), 8.43 (dd, J = 8.2, 2.4 Hz, 1H), 7.87 (brs, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.26 (d, J = 6.7 Hz, 1H), 7.10 – 6.98 (m, 3H), 6.90 (d, J = 7.5 Hz, 1H), 4.74-7.62 (m, 2H), 4.48 – 4.34 (m, 1H), 1.92 (s, 3H), 1.85-1.72 (m, 1H), 1.65 – 1.50 (m, 1H), 0.94 (t, J = 7.4 Hz, 3H) ppm.
Example 44 Method B		Method 4: 1.09 min, m/z, 495.1 [M+H] ⁺	δ 9.00 – 8.93 (m, 1H), 8.53 – 8.47 (m, 2H), 8.12 – 8.05 (m, 2H), 7.97 (d, J = 8.3 Hz, 1H), 7.57 (d, J = 6.8 Hz, 1H), 7.08 – 7.01 (m, 2H), 6.89 – 6.81 (m, 2H), 4.74 – 4.61 (m, 2H), 4.06 – 3.92 (m, 2H), 2.40 (s, 3H), 1.81 (s, 3H) ppm.
Example 45 Method B		Method 4: 1.19 min, m/z, 509.2 [M+H] ⁺	δ 8.95 – 8.86 (m, 1H), 8.53 – 8.46 (m, 2H), 8.11 – 8.05 (m, 2H), 8.00 – 7.93 (m, 1H), 7.57 (d, J = 6.8 Hz, 1H), 7.08 – 6.98 (m, 2H), 6.89 – 6.81 (m, 2H), 4.71 – 4.55 (m, 3H), 2.39 (s, 3H), 1.81 (s, 3H), 1.29 (d, J = 6.9 Hz, 3H) ppm.
Example 46 Method B		Method 4: 1.18 min, m/z, 509.2 [M+H] ⁺	δ 8.96 – 8.86 (m, 1H), 8.54 – 8.46 (m, 2H), 8.12 – 8.05 (m, 2H), 8.01 – 7.94 (m, 1H), 7.57 (d, J = 6.8 Hz, 1H), 7.09-6.98 (m, 2H), 6.89-6.80 (m, 2H), 4.72 – 4.56 (m, 3H), 2.39 (s, 3H), 1.81 (s, 3H), 1.29 (d, J = 6.9 Hz, 3H) ppm.
Example 47 Method B		Method 3: 3.38 min, m/z, 544.4 [M+H] ⁺	δ 10.81 (s, 1H), 9.54 – 9.50 (m, 1H), 9.32 (s, 1H), 9.17 – 9.14 (m, 1H), 8.68 (d, J = 6.9 Hz, 1H), 8.49 (s, 1H), 8.06 (d, J = 6.9 Hz, 1H), 7.85 – 7.78 (m, 2H), 7.74 – 7.67 (m, 2H), 7.24 – 7.17 (m, 2H), 7.17 – 7.10 (m, 1H), 6.97 (d, J = 7.6 Hz, 1H), 4.87 (s, 2H), 2.00 (s, 3H) ppm.
Example 48 Method B		Method 4: 0.83 min, m/z, 477.1 [M+H] ⁺	δ 10.82 (s, 1H), 9.52 – 9.49 (m, 1H), 9.19 (br s, 1H), 9.14 (d, J = 1.2 Hz, 1H), 8.86 (s, 1H), 8.66 (d, J = 7.0 Hz, 1H), 8.46 – 8.32 (m, 2H), 8.15 – 8.09 (m, 1H), 8.01 (d, J = 6.9 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.22 – 7.10 (m, 3H), 6.97 (d, J = 7.5 Hz, 1H), 4.88 (s, 2H), 1.99 (s, 3H) ppm.

Example 49 Method B		Method 4: 0.77 min, m/z. 477.2 [M+H] ⁺ .	δ 11.77 (s, 1H), 9.49 (s, 1H), 9.13 (s, 1H), 9.01 (br s, 1H), 8.72 (d, J = 5.9 Hz, 2H), 8.64 (d, J = 7.0 Hz, 1H), 8.32 (br s, 1H), 8.02 (d, J = 6.5 Hz, 2H), 7.94 (d, J = 6.9 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.18 – 7.11 (m, 1H), 7.11 – 7.04 (m, 1H), 6.98 (d, J = 7.6 Hz, 1H), 4.99 (s, 2H), 1.99 (s, 3H) ppm.
Example 50 Method B		Method: 2.58 min, m/z, 495.4 [M+H] ⁺	δ 9.04 – 8.98 (m, 1H), 8.72 (s, 1H), 8.53 – 8.46 (m, 2H), 8.14 (s, 1H), 8.01 (s, 1H), 7.55 (d, J = 6.7 Hz, 1H), 7.07 – 7.00 (m, 2H), 6.89 – 6.81 (m, 2H), 4.73 – 4.61 (m, 2H), 4.06 – 3.90 (m, 2H), 2.21 (s, 3H), 1.81 (s, 3H) ppm.
Example 51 Method B		Method 3: 2.92 min, m/z. 509.3 [M+H] ⁺	δ 8.96 – 8.89 (m, 1H), 8.71 (d, J = 4.4 Hz, 1H), 8.53 – 8.46 (m, 2H), 8.14 (s, 1H), 8.01 (s, 1H), 7.55 (d, J = 6.8 Hz, 1H), 7.08 – 6.99 (m, 2H), 6.88 – 6.81 (m, 2H), 4.70 – 4.54 (m, 3H), 2.20 (s, 3H), 1.81 (s, 3H), 1.29 (d, J = 7.0 Hz, 3H) ppm.
Example 52 Method B		Method 3: 2.92 min, m/z. 509.4 [M+H] ⁺	δ 8.96 – 8.88 (m, 1H), 8.71 (d, J = 4.4 Hz, 1H), 8.53 – 8.46 (m, 2H), 8.14 (s, 1H), 8.01 (s, 1H), 7.55 (d, J = 6.7 Hz, 1H), 7.07 – 7.00 (m, 2H), 6.88 – 6.81 (m, 2H), 4.70 – 4.55 (m, 3H), 2.20 (s, 3H), 1.81 (s, 3H), 1.29 (d, J = 7.0 Hz, 3H) ppm.
Example 53 Method B		Method 3: 2.85 min, m/z. 495.4 [M+H] ⁺	δ 9.18 (s, 1H), 9.04 – 8.97 (m, 1H), 8.82 (d, J = 2.0 Hz, 1H), 8.56 (d, J = 7.0 Hz, 1H), 8.31 (d, J = 1.8 Hz, 1H), 8.06 (s, 1H), 7.34 (d, J = 6.8 Hz, 1H), 7.12 – 7.00 (m, 3H), 6.89 – 6.84 (m, 1H), 4.73 – 4.60 (m, 2H), 4.07 – 3.91 (m, 2H), 2.32 (s, 3H), 1.75 (s, 3H) ppm.
Example 54 Method B		Method 3: 2.95 min, m/z. 509.4 [M+H] ⁺	δ 9.30 (s, 1H), 8.93 (dd, J = 8.7, 3.9 Hz, 1H), 8.82 (d, J = 1.7 Hz, 1H), 8.58 (d, J = 7.0 Hz, 1H), 8.31 (d, J = 1.3 Hz, 1H), 8.14 (s, 1H), 7.38 (d, J = 6.8 Hz, 1H), 7.17 – 7.11 (m, 1H), 7.08 – 6.98 (m, 2H), 6.86 (d, J = 7.3 Hz, 1H), 4.72 – 4.55 (m, 3H), 2.31 (s, 3H), 1.75 (s, 3H), 1.30 (dd, J = 6.9, 2.9 Hz, 3H) ppm.

Example 55 Method B		Method 3: 2.95 min, m/z, 509.4 [M+H] ⁺	δ 9.17 (s, 1H), 8.97 – 8.89 (m, 1H), 8.82 (d, J = 1.4 Hz, 1H), 8.56 (d, J = 7.0 Hz, 1H), 8.33 – 8.28 (m, 1H), 8.05 (s, 1H), 7.33 (d, J = 6.8 Hz, 1H), 7.11 – 6.98 (m, 3H), 6.86 (d, J = 7.2 Hz, 1H), 4.70 – 4.56 (m, 3H), 2.31 (s, 3H), 1.75 (s, 3H), 1.30 (dd, J = 6.9, 2.7 Hz, 3H), ppm
Example 56 Method B		Method 3: 2.98 min, m/z, 510.4 [M+H] ⁺	δ 9.28 (s, 1H), 8.97 – 8.90 (m, 1H), 8.61 – 8.51 (m, 2H), 8.15 (s, 1H), 7.79 (d, J = 6.9 Hz, 1H), 7.12 – 7.01 (m, 2H), 6.94 – 6.85 (m, 2H), 4.73 – 4.56 (m, 3H), 2.60 (s, 3H), 1.79 (s, 3H), 1.33 – 1.27 (m, 3H) ppm.
Example 57 Method B		Method 3: 2.85 min, m/z, 496.3 [M+H] ⁺	δ 9.28 (s, 1H), 9.05 – 8.98 (m, 1H), 8.59 – 8.53 (m, 2H), 8.14 (s, 1H), 7.79 (d, J = 6.7 Hz, 1H), 7.12 – 7.02 (m, 2H), 6.93 – 6.85 (m, 2H), 4.76 – 4.62 (m, 2H), 4.08 – 3.92 (m, 2H), 2.67 (s, 3H), 1.79 (s, 3H) ppm.

DDR1 and DDR2 Binding Assay Methods

The capacity of compounds to bind to DDR1 and DDR2 was quantified using a LanthaScreen Eu Kinase Binding Assay. Recombinant human DDR1 (2.5 nM; aa440-876 containing a GST tag) and DDR2 (1.75 nM; aa427-855 containing a GST tag) were diluted in assay buffer (50 mM HEPES pH7.3, 10 mM MgCl₂, 1 mM EGTA and 0.01% Tween) with various concentrations of compound in a 384-well plate and a volume of 5uL. After a 30-minute incubation at room temperature, 2.5 µL of Eu-anti GST antibody (diluted to 1 nM in assay buffer) plus Kinase Tracer 178 (diluted in assay buffer to 5 nM for DDR1 and 10 nM for DDR2) were added to the plate. Following 60-minute incubation at room temperature, time-resolved fluorescence was measured on a BMG Labtech PHERAstar plate reader. DMSO (1%) and reference compound (1 µM) were used to generate the Max and Min assay signals, respectively. Data was analysed using a four-parameter logistic model to calculate IC₅₀ values, with at least two independent replicates were performed for each compound.

Biological activity values

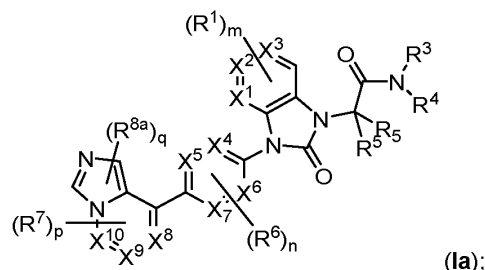
The following table (Table 14) shows the pIC₅₀ values for the above examples against the DDR1 and DDR2 kinases (A: pIC₅₀ > 8; B: 8 ≥ pIC₅₀ > 7; C: 7 ≥ pIC₅₀ > 6; D: pIC₅₀ ≤ 6; ND: not determined).

Table 14.

Example	DDR1 pIC ₅₀	DDR2 pIC ₅₀	Example	DDR1 pIC ₅₀	DDR2 pIC ₅₀	Example	DDR1 pIC ₅₀	DDR2 pIC ₅₀
1	B	D	24	A	C	48	B	D
2	B	C	25	A	C	49	B	D
3	B	D	26	B	C	50	B	C
4	D	D	27	A	C	51	B	C
5	C	D	28	B	D	52	C	D
6	A	C	29	D	D	53	B	D
7	B	C	30	B	D	54	B	C
8	A	B	31	C	D	55	C	D
9	A	C	32	C	D	56	B	C
10	A	C	33	B	C	57	B	C
11	B	D	34	B	D			
12	C	D	35	C	D			
13	A	C	36	A	C			
14	C	D	37	B	C			
15	B	D	38	B	D			
16	A	C	39	A	C			
17	A	C	40	B	D			
18	B	C	41	D	D			
19	D	D	42	B	D			
20	C	D	43	C	D			
21	C	D	44	B	C			
22	A	B	45	B	C			
23	A	C	46	C	D			
24	A	C	47	B	D			

CLAIMS

1. A compound of formula (Ia) or a pharmaceutically acceptable salt thereof:



- 5 wherein

X¹, X² and X³ are each independently selected from carbon and nitrogen, wherein at least two of X¹, X² and X³ are carbon;

X⁴, X⁵, X⁶ and X⁷ are each independently selected from carbon and nitrogen, wherein at least two of X⁴, X⁵, X⁶ and X⁷ are carbon;

- 10 X⁸, X⁹ and X¹⁰ are each independently selected from carbon and nitrogen, wherein at least two of X⁸, X⁹ and X¹⁰ are carbon;

R¹ is independently selected at each occurrence from halo, nitro, cyano, NR⁹R¹⁰, OR¹¹, SR⁹, SO₂NR⁹R⁹, SO₂R⁹, CO₂R⁹, C(O)R⁹, CONR⁹R⁹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl and cyclopropyl;

- 15 R³ is independently selected from H and C₁-C₄-alkyl;

R⁴ is independently selected from C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₀-C₄-alkylene-R^{4a}; wherein R^{4a} is independently selected from: C₃-C₈-cycloalkyl, phenyl, 5-, 6-, 9- or 10-membered heteroaryl and 4- to 10-membered heterocycloalkyl; wherein said heterocycloalkyl or heteroaryl group may be monocyclic or bicyclic; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with a single R¹² group and/or from 1 to 4 R¹³ groups and wherein said phenyl or heteroaryl group is optionally substituted with a single R¹² group and/or from 1 to 3 R¹⁴ groups;

- 20 or R³ and R⁴, together with the nitrogen atom to which they are attached together form a 4- to 10-membered heterocycloalkyl group or a 5-, or 9-membered heteroaryl group; wherein said heterocycloalkyl or heteroaryl group may be monocyclic or bicyclic; wherein said heterocycloalkyl group is optionally substituted with a single R¹² group and/or from 1 to 4 R¹³ groups and wherein said heteroaryl group is optionally substituted with a single R¹² group and/or from 1 to 3 R¹⁴ groups;

R⁵ is independently at each occurrence selected from H, halo and C₁-C₄-alkyl, or the two R⁵ groups and the carbon atom to which they are attached may together form a C₃-C₆ cycloalkyl ring;

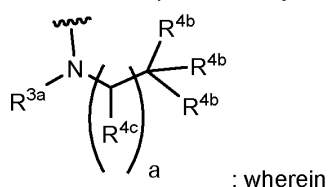
- 25 R⁸ is independently at each occurrence selected from halo, nitro, cyano, NR⁹R¹⁰, OR¹¹, SR⁹, SO₂NR⁹R⁹, SO₂R⁹, CO₂R⁹, C(O)R⁹, CONR⁹R⁹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl and cyclopropyl;

- R⁷ is independently at each occurrence selected from halo, nitro, cyano, NR⁹R¹⁰, OR¹¹, SR⁹, SO₂NR⁹R⁹, SO₂R⁹, CO₂R⁹, C(O)R⁹, CONR⁹R⁹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl and cyclopropyl;
- R^{8a} is independently selected from halo, nitro, cyano, NR⁹R¹⁰, OR¹¹, SR⁹, SO₂NR⁹R⁹, SO₂R⁹, CO₂R⁹, C(O)R⁹, CONR⁹R⁹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₁-C₄-alkyl substituted with OR¹¹, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl and C₀-C₄-alkylene-R^{8c};
- R^{8c} is independently selected from C₃-C₆-cycloalkyl and 3- to 7-membered heterocycloalkyl; wherein said heterocycloalkyl group is attached to the C₀-C₄-alkylene via a carbon atom in the heterocycloalkyl ring; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R¹³ groups;
- R⁹ is independently at each occurrence selected from H and C₁-C₄-alkyl; or two R⁹ groups, together with the nitrogen atom to which they are attached together form a C₅-C₈-heterocycloalkyl group optionally substituted with from 0 to 4 R¹⁵ groups;
- R^{9a} is independently at each occurrence selected from H and C₁-C₄-alkyl;
- R¹⁰ is independently at each occurrence selected from H, C₁-C₄-alkyl, C(O)-C₁-C₄-alkyl and S(O)₂-C₁-C₄-alkyl; or R⁹ and R¹⁰, together with the nitrogen atom to which they are attached together form a C₅-C₈-heterocycloalkyl group optionally substituted with from 0 to 4 R¹⁵ groups;
- R¹¹ is independently at each occurrence selected from H, C₁-C₄-alkyl, C(O)-C₁-C₄-alkyl and C₁-C₄-haloalkyl;
- R¹² is independently selected from C₃-C₆-cycloalkyl, phenyl, 5- or 6- membered heteroaryl and 3- to 6-membered-heterocycloalkyl; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R¹³ groups and wherein said phenyl or heteroaryl group is optionally substituted with from 1 to 3 R¹⁴ groups;
- R¹³ is independently at each occurrence selected from =O, halo, nitro, cyano, NR⁹R¹⁰, OR¹¹, SR⁹, SO₂NR⁹R⁹, CO₂R⁹, C(O)R⁹, CONR⁹R⁹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with OR¹¹, C₁-C₄-alkyl substituted with NR⁹R¹⁰, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl, C₆-C₁₀-aryl, and C₃-C₆-cycloalkyl;
- R¹⁴ is independently at each occurrence selected from halo, nitro, cyano, NR⁹R¹⁰, OR¹¹, SR⁹, SO₂R⁹, SO₂NR⁹R¹⁰, CO₂R⁹, C(O)R⁹, CONR⁹R⁹, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl, C₁-C₄-alkyl substituted with OR¹¹, C₁-C₄-alkyl substituted with NR⁹R¹⁰ and cyclopropyl;
- R¹⁵ is independently at each occurrence selected from =O, halo, nitro, cyano, NR^{9a}R¹⁰, OR¹¹, SR⁹, SO₂NR^{9a}R⁹, CO₂R⁹, C(O)R⁹, CONR^{9a}R⁹, C₁-C₄-alkyl, C₁-C₄-alkyl substituted with OR¹¹, C₁-C₄-alkyl substituted with NR^{9a}R¹⁰, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₁-C₄-haloalkyl, C₆-C₁₀-aryl, and C₃-C₆-cycloalkyl;
- m is an integer selected from 0, 1, 2, 3 and 4;
- n is an integer selected from 0, 1, 2, 3 and 4;
- p is an integer selected from 0, 1, 2 and 3;
- q is an integer selected from 0, 1 and 2

wherein any of the aforementioned alkyl, alkylene or cyclopropyl groups is optionally substituted, where chemically possible, by 1 to 5 substituents which are each independently at each occurrence selected from the group consisting of: halo, oxo, fluoro, nitro, cyano, NR^aR^b, OR^a, SR^a, CO₂R^a,

C(O)R^a, CONR^aR^a, C₁-C₄-alkyl, C₁-C₄-haloalkyl and cyclopropyl; wherein R^a is independently at each occurrence selected from H, C₁-C₄-alkyl and C₁-C₄-haloalkyl; and R^b is independently at each occurrence selected from H, C₁-C₄-alkyl, C(O)-C₁-C₄-alkyl and S(O)₂-C₁-C₄-alkyl.

2. A compound of claim 1, wherein m is 0 or 1.
- 5 3. A compound of claim 1, wherein m is at least 1, X¹ is carbon and an R¹ group is attached to the X¹ carbon.
4. A compound of claim 1 or claim 2, wherein n is 0 or 1.
5. A compound of any one of claims 1 to 3, wherein p is 0.
6. A compound of any one of claims 1 to 4, wherein q is 0.
- 10 7. A compound of any one of claims 1 to 5, wherein R⁵ is at each occurrence H.
8. A compound of any one of claims 1 to 7, wherein X¹, X² and X³ are each carbon.
9. A compound of any one of claims 1 to 8, wherein X⁴, X⁵, X⁶ and X⁷ are each carbon.
10. A compound of any one of claims 1 to 8, wherein at least one of X⁴, X⁵, X⁶, and X⁷ is nitrogen.
11. A compound of any one of claims 1 to 10, wherein X⁸, X⁹ and X¹⁰ are each carbon.
- 15 12. A compound of any one of claims 1 to 10, wherein a single one of X⁸, X⁹ and X¹⁰ is nitrogen.
13. A compound of any one of claims 1 to 12, wherein NR³R⁴ has the formula



a is an integer selected from 1 and 2;

R^{4b} is at each occurrence selected from H and F; wherein at least one R^{4b} group is F;

- 20 R^{3a} is independently selected from H and C₁-C₄-alkyl;

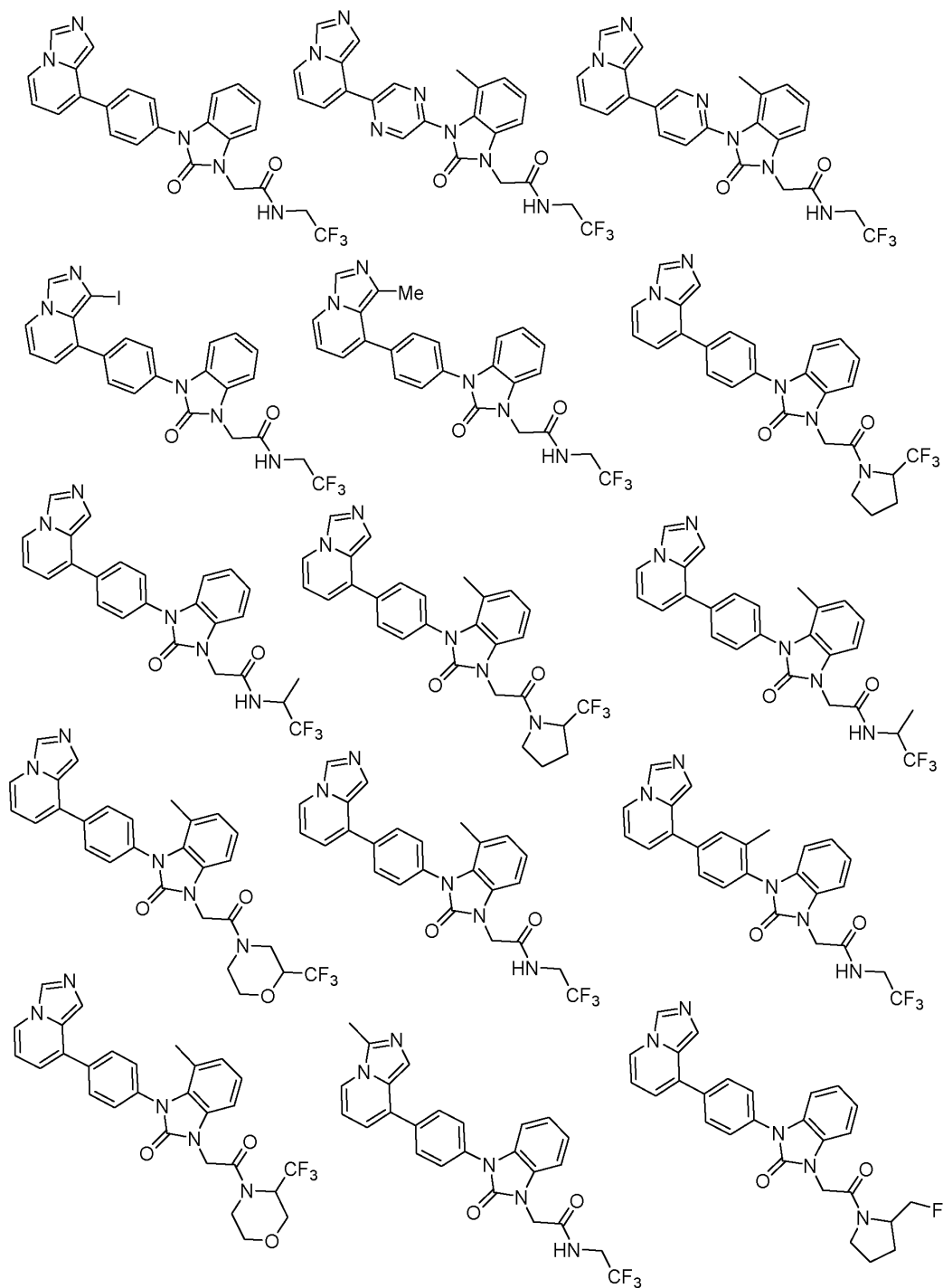
R^{4c} is independently at each occurrence selected from H, C₁-C₄-alkyl and C₄-C₆-cycloalkyl; or

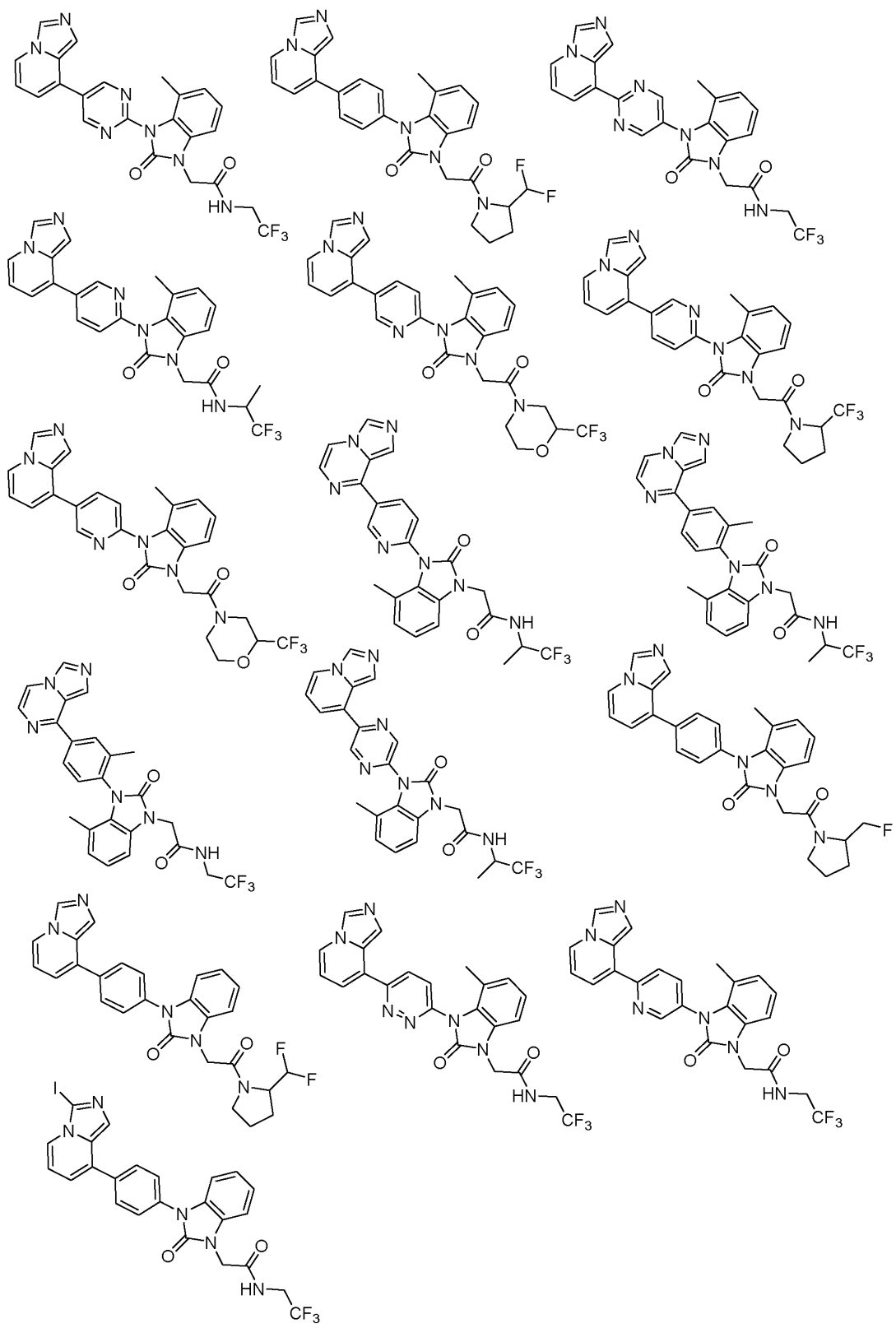
R^{3a} and a single R^{4c}, together with the carbon and nitrogen to which they are attached, form a 4- to 6-membered heterocycloalkyl group.

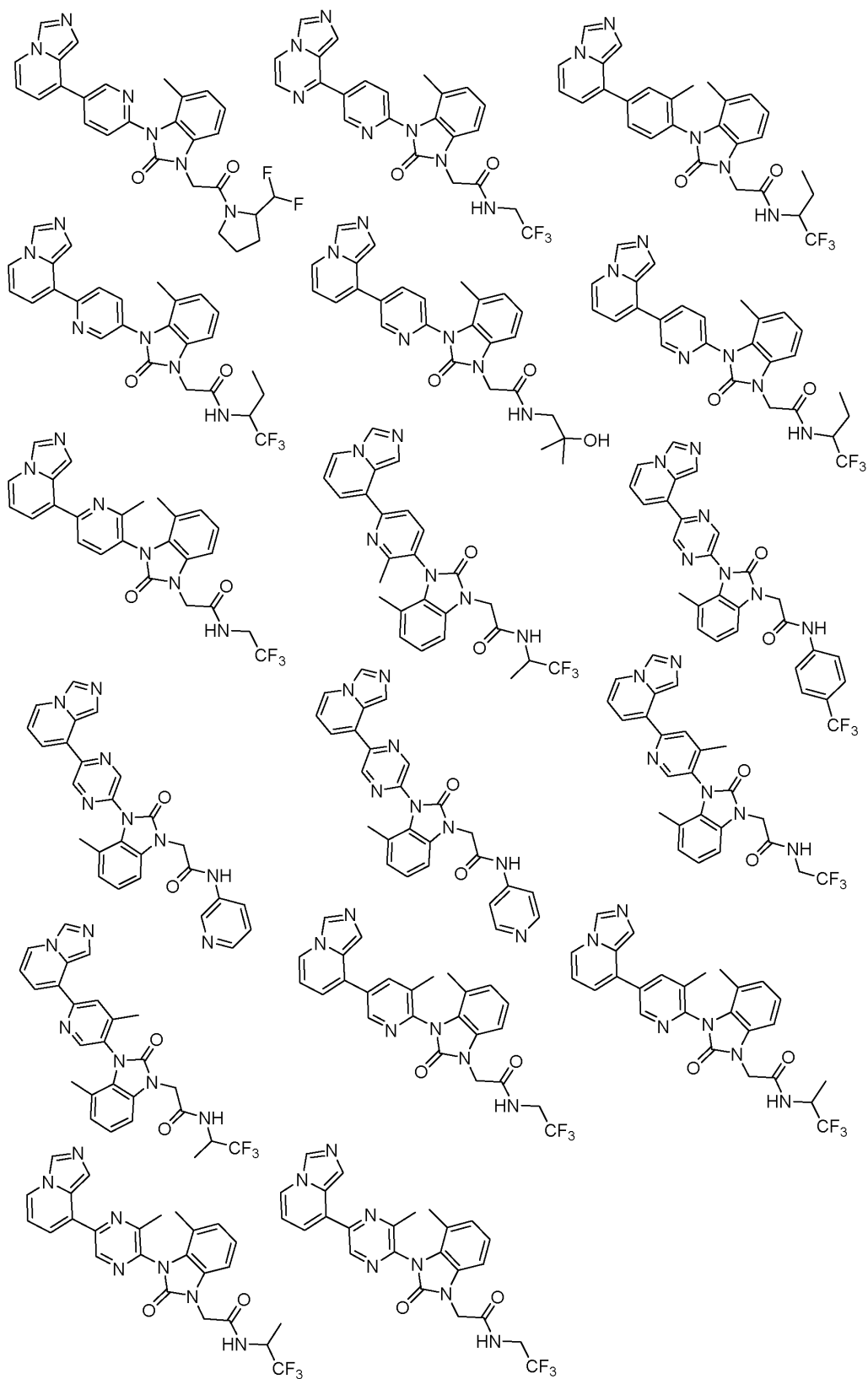
14. A compound of claim 13, wherein a is 1.
- 25 15. A compound of claim 13 or claim 14, wherein at least two R^{4b} groups are F.
16. A compound of any one of claims 13 to 15, wherein R^{3a} is H.
17. A compound of any one of claims 13 to 16, wherein R^{4c} is selected from H and C₁-C₄-alkyl.

18. A compound of any one of claims 13 to 15, wherein R^{3a} and R^{4c} , together with the carbon and nitrogen to which they are attached, form a 4- to 6-membered heterocycloalkyl group.

19. A compound of claim 1, wherein the compound of formula (I) is selected from:







20. A pharmaceutical formulation comprising a compound of any one of claims 1 to 19 and a pharmaceutically acceptable excipient.
 21. A compound of any one of claims 1 to 19 for use as a medicament.
 22. A compound of any one of claims 1 to 19 for use in treating a a disease or disorder selected
- 5 from renal conditions, liver conditions, inflammatory conditions, cardiovascular conditions, acute and chronic organ transplant rejection, fibrotic diseases and cancer.